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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ALEMBIC PHARMACEUTICALS LTD., Plaintiff, v. NOVARTIS PHARMACEUTICALS CORP. and NOVARTIS AG, Defendants.	Civil Action No. **FILED UNDER SEAL**

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff Alembic Pharmaceuticals Ltd. ("Alembic"), by and through its counsel, respectfully submits this Complaint for Declaratory Judgment against Defendants Novartis Pharmaceuticals Corp. ("Novartis Pharmaceuticals Corp.") and Novartis AG ("Novartis AG") (collectively "Novartis" or "Defendants") seeking a declaration that Alembic has not infringed, does not infringe, and will not infringe any valid claim of U.S. Patent No. 9,283,209 ("the '209

Patent"). Alembic brings this suit to obtain patent certainty under 21 U.S.C. § 355(j)(5)(C)(i)(I), and to obtain final FDA approval to market its low-cost, generic deferasirox drug products at the earliest possible date pursuant to 21 U.S.C. §355(j)(5)(D)(i)(I). Alembic seeks a declaratory judgment of non-infringement of the '209 Patent that would free the FDA to approve Alembic's generic drug application at the earliest-possible date, thereby allowing Alembic to market its low-cost, generic deferasirox drug products. Alembic alleges as follows:

NATURE AND SUMMARY OF THIS ACTION

1. This action arises under the patent laws of the United States and Amendments to the Federal Food, Drug, and Cosmetics Act (the "Hatch-Waxman Act"),[1] which govern the U.S. Food and Drug Administration's ("FDA") approval of both new and generic drugs. *See* 21 U.S.C. § 355 *et seq.*; 35 U.S.C. §§ 156, 217(e). Alembic seeks final FDA approval for the commercial manufacture, use, importation, offer for sale, and sale of a generic version of Jadenu®, 180 mg (deferasirox) tablets, as described in Alembic's Abbreviated New Drug Application ("ANDA") No. 211824 ("Alembic's ANDA"). Alembic's ANDA contains a certification, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certification"), that the '209 Patent will not be infringed by the manufacture, use, or sale of Alembic's 180 mg deferasirox tablets.

2. In accordance with 21 U.S.C. § 355(j)(2)(B) and 21 C.F.R. § 314.95, Alembic sent notice to Defendants of Alembic's Paragraph IV certification to the '209 Patent and provided an Offer of Confidential Access to its ANDA No. 211824 on June 4, 2018 ("Alembic's Notice Letter"). *See* Exhibit I, 69-72. Novartis did not request a copy of Alembic's ANDA and

[1] Drug Price Competition and Patent Term Restoration Act, 21 U.S.C. § 355(j) (1984).

chose not to bring a suit for patent infringement, even though they had an opportunity to do so. *See* 21 U.S.C. § 355(j)(5)(C).

3. The Hatch-Waxman Act provides for a "civil action to obtain patent certainty" when a generic applicant makes such certifications, and the patent owner does not bring an action within 45 days of receiving notice of the Paragraph IV certification. *See* 21 U.S.C. § 355(j)(5)(C)(i)(I)(aa)-(cc). This declaratory judgment provision in the Hatch-Waxman Act aims to encourage early resolution of patent disputes and prevent brand-name drug companies from using tactics that forestall the competing generic drug makers from entering the market. *See Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1285 (Fed. Cir. 2008).

4. The Medicare Modernization Act of 2003 ("MMA") sets forth certain provisions by which first ANDA applicants would forfeit their exclusivity. For example, the entry of a final judgment of non-infringement with respect to the patents against which the first ANDA applicant filed Paragraph IV certifications, regardless of whether those patents are asserted against subsequent ANDA filers, will cause the first ANDA filer to forfeit its exclusivity. 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(AA).

5. Alembic's complaint seeks a judgment to obtain patent certainty that Alembic's 180 mg deferasirox tablets do not infringe any valid and enforceable claim of the '209 Patent. Such judgment would trigger forfeiture of the first ANDA applicant's 180-day exclusivity, which presently blocks the FDA from approving Alembic's ANDA, thereby enabling Alembic to bring its 180 mg deferasirox tablets to market at the earliest possible date allowed under applicable statutory and FDA regulatory provisions.

THE PARTIES

6. Plaintiff Alembic is a corporation organized and existing under the laws of the India, with a place of business at Alembic Road, Vadodara 390003, Gujarat, India.

7. On information and belief, Defendant Novartis Pharmaceuticals Corp. is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business in East Hanover, New Jersey.

8. On information and belief, Defendant Novartis AG is a corporation organized and existing under the laws of Switzerland and has its principal place of business in Basel, Switzerland.

9. Based on publicly available information, Novartis AG is the owner and assignee of record with the United States Patent and Trademark Office ("USPTO") of the '209 Patent.

JURISDICTION AND VENUE

10. This is a Complaint for a declaratory judgment that Alembic has not, does not, and will not infringe the claims of the '209 Patent, which arises under the patent laws of the United States, 35 U.S.C. §§ 1 *et seq.*, the Hatch-Waxman Act, 21 U.S.C. §§ 355(j) *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

11. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a) because this action involves substantial claims arising under the United States Patent Act (35 U.S.C. §§ 1 *et seq.*), the Declaratory Judgment Act (28 U.S.C. §§ 2201-2202), 21 U.S.C. § 355(j)(5)(C), and 35 U.S.C. § 271(e)(5).

12. An actual controversy exists between Alembic and Novartis by virtue of Novartis' listing of the '209 Patent in the Orange Book for Jadenu®, Alembic's filing of ANDA No. 211824 with the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(j), for a generic version of 180 mg deferasirox tablets that are bioequivalent to Novartis' drug Jadenu®, and Novartis' failure to bring suit against Alembic in connection with Alembic's filing of ANDA No. 211824 or any product described therein. Additionally, another applicant was the first to submit an ANDA referencing the 180 mg strength of Jandenu®, and therefore

retains eligibility for 180-day marketing exclusivity, which indefinitely blocks approval of any subsequently filed ANDA, such as Alembic's. Only a final decision of noninfringement or invalidity of the '209 Patent will lift that regulatory block. *See Apotex, Inc. et al v. Daiichi Sankyo, Inc. et al*, 781 F.3d 1356, 1368–1369 (Fed. Cir. 2015).

13. Alembic contends that it has a right to engage in making, using, offering to sell, and selling its product described in Alembic's ANDA without license from Novartis.

14. This Court has personal jurisdiction over Novartis Pharmaceuticals Corp. because, on information and belief, Novartis Pharmaceuticals Corp. has a principal place of business in East Hanover, New Jersey and conducts substantial business in, and has regular and systematic contact with, the State of New Jersey, including this District. On information and belief, Novartis Pharmaceuticals Corp. has purposefully availed itself to this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New Jersey and deriving revenue from such activities.

15. On information and belief, Novartis Pharmaceuticals Corp. has sued for patent infringement in this District, and has therefore availed itself to this forum, in at least the following cases: *Novartis Pharmaceuticals Corporation et al v. Actavis, Inc. et al*, Civ. No. 15-8978 (D.N.J. Dec. 31, 2015); *Novartis Pharmaceuticals Corporation et al v. Aurobindo Pharma Ltd. et al*, Civ. No. 15-4427 (D.N.J. Jan. 25, 2015); *Novartis Pharmaceuticals Corporation et al v. Sagent Pharmaceuticals, Inc.*, Civ. No. 14-cv-7556 (D.N.J. Dec. 3, 2014); *Novartis Pharmaceuticals Corporation et al v. Dr. Reddy's Lab's, Ltd. et al*, Civ. No. 15-7964 (D.N.J. Nov. 6, 2015).

16. This Court has personal jurisdiction over Novartis AG based on, *inter alia*, Novartis AG's systemic and continuous contacts with New Jersey, including this District. Upon information and belief, Novartis AG has conducted and continues to conduct business directly or through, *inter alia*, its subsidiaries, agents, and alter egos, including Novartis Pharmaceuticals Corp., in this District. On information and belief, Novartis AG has purposefully availed itself to this forum by, among other things, making, shipping, using, offering to sell or selling, or causing others to use, offer to sell, or sell, pharmaceutical products in the State of New Jersey and deriving revenue from such activities.

17. On information and belief, Novartis AG has sued for patent infringement in this District, and has therefore availed itself to this forum, in at least the following cases: *Novartis AG v. Apotex Inc.*, Civ. No. 09-5614 (D.N.J. Jan. 24, 2011); *Novartis AG et al v. Aurobindo Pharma Ltd. et al*, Civ. No. 17-389 (D.N.J. Jan 19, 2017); *Novartis AG et al v. HEC Pharm. Co., Ltd. et al*, Civ. No. 15-1647 (D.N.J. Mar. 5, 2015); *Novartis AG et al v. Actavis, Inc. et al*, Civ. No. 14-7849 (D.N.J. Dec. 14, 2014); *Novartis AG et al v. Teva Pharmaceuticals USA, Inc. et al*, Civ. No. 11-2289 (D.N.J. Apr. 21, 2011).

18. Novartis AG has also consented to personal jurisdiction in this district in related actions involving generic versions of Jadenu® and the '209 Patent. *See Piramal HealthCare UK Ltd. v. Novartis AG and Novartis Pharm. Corp.*, No. 19-12651, D.I. 12-1, Exhibit G, 52, ¶ 3, July 8, 2019 Email From Tim Cook (D.N.J. filed July 22, 2019) ("Novartis AG has not contested personal jurisdiction in the District of New Jersey to the extent it is properly served.").

19. This Court also has personal jurisdiction over Novartis AG because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Alembic's claims arise under federal law, (b) Novartis AG is a foreign corporation (to the extent Novartis AG asserts

that it is not subject to personal jurisdiction in the courts of any state), and (c) Novartis AG has sufficient contacts with the United States as a whole, including but not limited to, contacts with the United States through Novartis AG's subsidiaries, agents, and alter egos, including Novartis Pharmaceuticals Corp., directing the manufacture, importation, offer for sale, and/or sale of pharmaceutical products that are distributed throughout the United States,, applying for and obtaining patents in the United States, and litigating cases in United States courts. *See Novartis AG v. Apotex Inc.*, Civ. No. 09-5614 PGS, 2011 WL 691594 (D.N.J. Jan. 24, 2011); *Novartis AG et al. v. HEC Pharm Co., Ltd. et al.*, Civ. No. 15- 00151, (D. Del filed Feb 11, 2015).

20. Venue is proper in this Court pursuant to 28 U.S.C. §1391.

HATCH-WAXMAN ACT OVERVIEW

21. In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, commonly referred to as the Hatch-Waxman Act. *See* 21 U.S.C. §355 and 35 U.S.C. §§ 156 and 271(e). The Hatch-Waxman Act was intended to encourage generic-drug competition while leaving intact incentives for research and development of new drugs by "branded" drug companies. *See* H.R. Rep No. 98-857, pt. 1 at 14-15 (1984). The Hatch-Waxman Act was designed to stem the rising cost of prescription drugs by bringing less expensive generic drugs to market faster.

22. To accomplish this goal, the Hatch-Waxman Act established a framework with five elements that are pertinent here.

23. First, a company seeking FDA approval of a new drug must submit a New Drug Application ("NDA") to the FDA. *See* 21 U.S.C. § 355. A brand-name drug sponsor must also inform the FDA of every patent that claims the "drug" or "method of using [the] drug" for which a claim of patent infringement could reasonably be asserted against unlicensed manufacture, use, or sale of that drug product. *See* 21 U.S.C. § 355(b)(1); 21 U.S.C. § 355(c)(2); 21 C.F.R. §

314.53(b), (c)(2). Upon approval of the NDA, the FDA publishes a listing of patent information for the approved drug in a document referred to as the Orange Book. *See* 21 U.S.C. § 355(b)(1). The new FDA-approved drug is known as the "reference-listed drug."

24. Second, the Hatch-Waxman Act provides a streamlined process for approving generic drugs. Before marketing a generic version of an FDA-approved drug, a generic-drug manufacturer must submit an ANDA to the FDA. An ANDA is "abbreviated" because applicants are generally not required to include the extensive preclinical and clinical data that must be included in an NDA for a brand-name drug. Instead, the ANDA applicants can rely on the NDA's preclinical and clinical data if the proposed generic product is "bioequivalent" to the corresponding reference-listed drug. *See* 21 U.S.C. § 355(j)(4)(F).

25. An ANDA must also contain one of four certifications for each patent listed in the Orange Book: (i) that there are no patents listed in the Orange Book; (ii) that any listed patent has expired; (iii) that the patent will expire before the generic manufacturer is seeking to market its generic product; or (iv) that the patent is invalid, unenforceable or will not be infringed by the manufacture, use or sale of the generic drug for which the ANDA is submitted. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV); 21 C.F.R. § 314.94(a)(12). The last of these is commonly referred to as a "Paragraph IV certification."

26. An applicant submitting an ANDA containing a Paragraph IV certification must provide formal written notice (*i.e.*, a "Notice Letter") informing both the patent holder and the NDA holder of its Paragraph IV certification. *See* 21 U.S.C. § 355(j)(2)(B)(i).

27. Third, the Hatch-Waxman Act encourages prompt resolution of patent disputes by authorizing a patent owner to sue an ANDA applicant for patent infringement if a Paragraph IV certification has been made. *See* 35 U.S.C. § 271(e)(2). By statute, if the patent owner brings suit

within 45-days of receiving notice of the Paragraph IV certification, the suit will trigger an automatic statutory 30-month stay of approval by the FDA of the ANDA to allow parties time to adjudicate the merits of the infringement action before the generic company launches its product. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

28. Fourth, to encourage prompt generic-market entry, the Hatch-Waxman Act grants the first generic applicant to file a substantially complete ANDA containing a Paragraph IV certification ("first-filer") to an Orange-Book-listed patent a 180-day period of marketing exclusivity that begins only upon the date it begins commercial marketing of its generic-drug product.

29. Fifth, to curb abuses of the 180-day exclusivity by patent owners and first-filers, where the 180-exclusivity is used to block all subsequent ANDA filers from obtaining approval of their respective ANDAs, Congress enacted the Medicare Modernization Amendments to the Hatch-Waxman Act, which provided for various conditions under which a first-filer would forfeit 180-day eligibility. *See* 21 U.S.C. § 355(j)(5)(D). The first of the forfeiture provisions, known as the Failure to Launch provision, provides that 180-day eligibility will be forfeited if a subsequent ANDA filer obtains a judgment of noninfringement to the patent(s) that confer exclusivity. *See* 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(AA); *see also Daiichi Sankyo*, 781 F.3d at 1360. As part of that remedy, the Hatch-Waxman Act allows ANDA applicants to bring declaratory-judgment actions asserting noninfringement against any relevant Orange-Book-listed patent if (1) neither the patent owner nor the NDA holder brought an action for infringement of the patent within the 45-day period; and (2) the ANDA applicant's notice of Paragraph IV certification included an offer of confidential access to the ANDA. 21 U.S.C. § 355(j)(5)(C)(i)(I)(aa)-(cc).

30. If the first-filer does not commercially market the generic drug and none of the MMA forfeiture provisions are triggered (including the entry of a final judgment of non-infringement or invalidity), the first-filer's 180-day exclusivity period will be delayed indefinitely, ultimately blocking final FDA approval of all subsequent ANDAs. This block is known as "bottlenecking" or a "statutory block" of a subsequent ANDA.

31. By authorizing declaratory judgment actions under these circumstances, Congress intended that full generic competition would not be delayed indefinitely by the first-filer's 180-day exclusivity. A declaratory judgment action by a subsequent ANDA applicant can result in a court decision that triggers forfeiture of the first-filer's 180-day exclusivity under 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(AA), thereby clearing the way for approval of a subsequent-filer's ANDA.

32. Congress explained the need for civil actions to obtain patent certainty:

> [W]hen generic applicants are blocked by a first generic applicant's 180-day exclusivity, the brand drug company could choose not to sue those other generic applicants so as to delay a final court decision that could … force the first generic to market. In … these … circumstances, generic applicants must be able to seek a resolution of disputes involving all patents listed in the Orange Book with respect to the drug.

Caraco, 527 F.3d at 1285 (quoting 149 Cong. Rec. S15885 (Nov. 25, 2003) (remarks of Sen. Kennedy, ranking member of U.S. Senate Committee on Health, Education, Labor, and Pensions)).

DEFENDANTS BLOCK ALEMBIC'S GENERIC ENTRY

1. The FDA's Orange Book Lists the '209 Patent

33. Novartis requested that the FDA list the '209 Patent in the Orange Book in connection with its Jadenu® NDA as a patent to which "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or

sale of the drug" product containing 90 mg, 180 mg, and 360 mg deferasirox in a tablet. 21 U.S.C. § 355(b)(1), (c)(2).

34. Novartis is the holder of the approved Jadenu® NDA No. 206910, and caused or authorized the '209 Patent to be listed in the Orange Book in connection with the Jadenu® NDA.

35. The '209 Patent, entitled "Oral Formulations of Deferasirox," issued on March 15, 2016. The patent names Indrajit Ghosh and Jia-Ai Zhang as inventors and identifies Novartis AG as the assignee of record. A true and correct copy of the '209 Patent is attached hereto as Exhibit A.

36. The '209 Patent purports to claim reduced and fast release orally administrable formulations of deferasirox.

37. At the time of Alembic's ANDA filing, two patents were listed in FDA's Orange Book as covering Jadenu®: U.S. Patent No. 6,465,504 ("the '504 patent") and the '209 Patent. Under the Hatch-Waxman statutory scheme, Alembic was required to submit patent certification to the '504 and '209 Patents.

38. Alembic's ANDA No. 211824 contains a Paragraph III certification to the '504 patent certifying Alembic would wait until the expiration of the '504 patent to begin marketing its ANDA Product. The '504 patent expired on April 5, 2019. Alembic's ANDA contains a Paragraph IV certification that Alembic's 180 mg deferasirox tablets will not infringe the '209 Patent, which does not expire until November 21, 2034. Through the Paragraph IV certification, Alembic is seeking immediate approval of its 180 mg deferasirox tablets, prior to expiration of the '209 Patent. Because Novartis chose not to sue Alembic asserting the '209 Patent, Alembic would have received final approval of its 180 mg deferasirox tablets but for the block presented by the first-filer's exclusivity, as discussed below.

2. The First Paragraph IV Certification for Jadenu®

39. Separate 180-day exclusivity periods are available for each strength of the same drug product because each strength is a distinct drug product. *See Apotex, Inc. v. Shalala*, 53 F. Supp. 2d 454, 456 (D.D.C. 1999) (citing FDA conclusion that "each strength of drug product is a separately listed drug.") Thus, an applicant must obtain forfeiture for each drug strength.

40. The FDA maintains the identity of ANDA first-filer(s) as confidential. However, the FDA publishes the date of submission of the first substantially complete ANDA containing a Paragraph IV certification for each drug. For Jadenu®, the FDA identifies the date of submission of the first-filer(s) as October 19, 2015 for the 90 mg and 360 mg strengths of Jadenu®. *See* Exhibit B, 28.

41. Based on the FDA's Orange Book, as of October 19, 2015, the Orange Book did not identify the '209 Patent.

42. Based on the FDA's Orange Book, as of April 21, 2016, the '209 Patent had been submitted to the Orange Book.

43. Upon information and belief, the first-filer for the 90 mg and 360 mg strengths (submitted on October 19, 2015) has withdrawn its Paragraph IV certification and therefore has forfeited any 180-day exclusivity to which it may have been entitled. *See* Exhibit C, 29-31, Stipulation and Order of Dismissal Without Prejudice, D.I. 123, ¶ 2, *Novartis Pharms. Corp. v. Actavis, Inc.*, C.A. No. 15-1219-RGA (D. Del. entered Sept. 18, 2017).

44. On information and belief, the first-filer(s) for the 180 mg strength submitted a substantially complete ANDA containing a Paragraph IV certification for 180 mg deferasirox tablets on April 21, 2016, and thus holds eligibility for 180-day marketing exclusivity that prevents all subsequently filed ANDAs (like Alembic's ANDA) for 180 mg deferasirox tablets from receiving final approval. Absent a judgment by this Court on the '209 Patent, the first-

filer(s) will retain eligibility for 180-days of marketing exclusivity until (1) it launches its product or (2) upon expiration of the '209 Patent in November 2034, thereby blocking Alembic's market entry indefinitely.

3. Alembic Applies for FDA Approval of its Generic Deferasirox Tablets

45. Alembic submitted ANDA No. 211824 to the FDA on March 28, 2018, seeking approval for the commercial manufacture, use, importation, offer for sale, and sale of a generic version of 90 mg, 180 mg, and 360 mg Jadenu® deferasirox tablets. Alembic's ANDA contains a Paragraph IV certification that the '209 Patent will not be infringed by the manufacture, use, or sale of Alembic's deferasirox products. Alembic submitted its ANDA *after* April 21, 2016, and therefore is a "subsequent filer." As a subsequent filer, Alembic is blocked from marketing its 180 mg deferasirox product by the first-filer(s) exclusivity.

46. On June 4, 2018, Alembic sent notice to Novartis, as it was required by law, of Alembic's Paragraph IV certification regarding the '209 Patent in Alembic's ANDA and provided an Offer of Confidential Access to its ANDA No. 211824 pursuant to 21 U.S.C. § 355(j)(2)(B)(i). *See* Exhibit I, 69-72.

47. Novartis received Alembic's Notice Letter on June 5 and 6, 2018. *See* Exhibit J, 77-78.

48. In its Notice Letter, Alembic provided to Novartis a detailed factual and legal basis for Alembic's Paragraph IV certification to the '209 Patent, explaining why the patent would not be infringed by Alembic's proposed generic 90 mg, 180 mg, and 360 mg deferasirox tablets. *See id.*, at 71. Novartis had a statutory right to bring suit against Alembic if it believed that Alembic infringed the '209 Patent, but Novartis chose not to sue Alembic. 21 U.S.C. § 355(j)(5)(B)(iii). Having failed to sue Alembic within a 45-day period following receipt of

Alembic's Notice Letter, the relevant statute provides Alembic with a statutory right to bring the present declaratory judgment action for patent certainty. 21 U.S.C. § 355(j)(5)(C)(i)(I)(aa)-(cc).

4. Alembic's Approval is Blocked

49. Alembic is prepared to begin commercial marketing of its deferasirox tablets upon FDA marketing approval, and has done so for the 90 mg and 360 mg strength tablets. Alembic's 180 mg strength deferasirox tablets, however, have received only tentative approval and are blocked from receiving final approval and entering the market until the end of the first-filer's exclusivity based on the '209 Patent. *See* Exhibit H, 59-66.

50. [redacted] Thus, FDA determined that the commercial launch of Alembic's 180 mg deferasirox tablets is indefinitely blocked until the expiration of the first filer's exclusivity.

51. As a consequence, absent a judgment from this Court declaring that Alembic's 180 mg deferasirox tablets do not infringe the '209 Patent, Alembic is unable to market its 180 mg deferasirox tablets indefinitely, thereby injuring Alembic by depriving it of sales revenue and profits that it could earn for that period of time. *See* 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb).

AN ARTICLE III CASE OR CONTROVERSY EXISTS

52. According to publicly available information, the first-filer has forfeited exclusivity for the 90 mg and 360 mg strengths of deferasirox tablets. *See* Exhibit B, 28.

53. There is an actual and ongoing controversy between Alembic and Novartis with respect to infringement of the ’209 Patent that can be resolved by a declaratory judgment from this Court. A judgment of non-infringement from this Court will trigger forfeiture of the first-filer’s exclusivity, as Congress intended under 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb), with respect to the 180 mg strength of deferasirox tablets, thereby allowing Alembic to bring its generic 180 mg deferasirox tablets to market at the earliest possible date, and enhancing generic competition.

54. The present dispute between Alembic and Novartis satisfies the three-part framework for determining whether an action presents a justiciable Article III controversy: (1) the plaintiffs have standing; (2) the issues are ripe for adjudication; and (3) the case is not rendered moot. *Caraco*, 527 F.3d at 1278.

55. Standing requires three elements: (1) an alleged injury in fact—“a harm suffered by the plaintiff that is ‘concrete’ and actual or imminent, not ‘conjectural’ or ‘hypothetical’”; (2) causation—“a fairly traceable connection between the plaintiff’s injury and the complained-of conduct of the defendant”; and (3) redressability—“a likelihood that the requested relief will redress the alleged injury.” *Caraco*, 527 F.3d at 1291.

56. Alembic is being injured in fact by the ongoing listing of Defendants’ ’209 Patent in FDA’s Orange Book. The ’209 Patent confers 180-day exclusivity eligibility for the first-filer, which serves to preclude Alembic from marketing its non-infringing generic deferasirox tablets at the earliest possible date. Alembic’s injury is unique in the Hatch–Waxman context as compared to ordinary infringement action: “Ordinarily, a potential competitor in other fields is legally free to market its product in the face of an adversely-held patent. In contrast, under the Hatch-Waxman Act, an ANDA filer is not legally free to enter the market without FDA

approval." *Id.* Novartis' listing of the '209 Patent in the Orange Book creates the bottleneck to Alembic's ANDA causing injury-in-fact to Alembic. *Id*.

57. Alembic's injury is directly traceable to Novartis, not the Hatch-Waxman Act or the FDA regulations. For example, the following facts, each traceable to Novartis, are the reasons for Alembic's injury: (1) Novartis chose not to sue Alembic after receiving a notice of Alembic's Paragraph IV certification, so as to avoid an adverse judgment on the '209 Patent; and (2) to date, Novartis has never asserted the '209 Patent, so as to avoid an adverse judgment. Novartis' actions are precisely the sort of "gaming" the system that the civil action to obtain a patent certainty was designed to prevent.

58. But for Novartis' attempts to avoid litigating the infringement of the '209 Patent, final approval of Alembic's 180 mg deferasirox tablets would not be independently and artificially delayed. But for Novartis' actions to delay resolution of the '209 Patent, Alembic's market entry for its 180 mg deferasirox tablets would not be delayed by the first-filer's 180-day exclusivity.

59. Alembic's injury is redressable: judgment of non-infringement or invalidity of the '209 Patent from this Court will activate forfeiture of the first-filer's exclusivity period as Congress intended, allowing Alembic to enter the market with its 180 mg deferasirox tablets at the earliest possible date and obtain patent certainty.

60. Accordingly, there is an actual, substantial, and continuing justiciable case and controversy between Alembic and Defendants over which this Court can and should exercise jurisdiction and declare the rights of the parties. *Caraco*, 527 F.3d at 1278.

61. Whether an action is "ripe" requires an evaluation of "both the fitness of the issues for judicial decision and the hardship to the parties of withholding court consideration." *Id*

at 1294. Alembic satisfies both prongs for ripeness. *First*, additional factual development would not advance the district court's ability to decide Alembic's action because Alembic's ANDA has all the necessary information to determine whether Alembic's deferasirox products infringe the '209 Patent. *Second*, Alembic will not be able to obtain patent certainty to market its 180 mg deferasirox tablets at the earliest possible date without a declaratory judgment, a hardship that creates the potential for substantial lost revenue.

62. The mootness doctrine requires that the parties must maintain a requisite personal stake. Alembic's 180 mg deferasirox tablets are being blocked from the market indefinitely. Only a judgment from this Court—either through adjudication or by consent decree—can alleviate the harm to Alembic and the public.

ALEMBIC'S 180 MG DEFERASIROX TABLETS

63. According to Alembic's ANDA No. 211824, Alembic's 180 mg deferasirox tablets have the following composition:

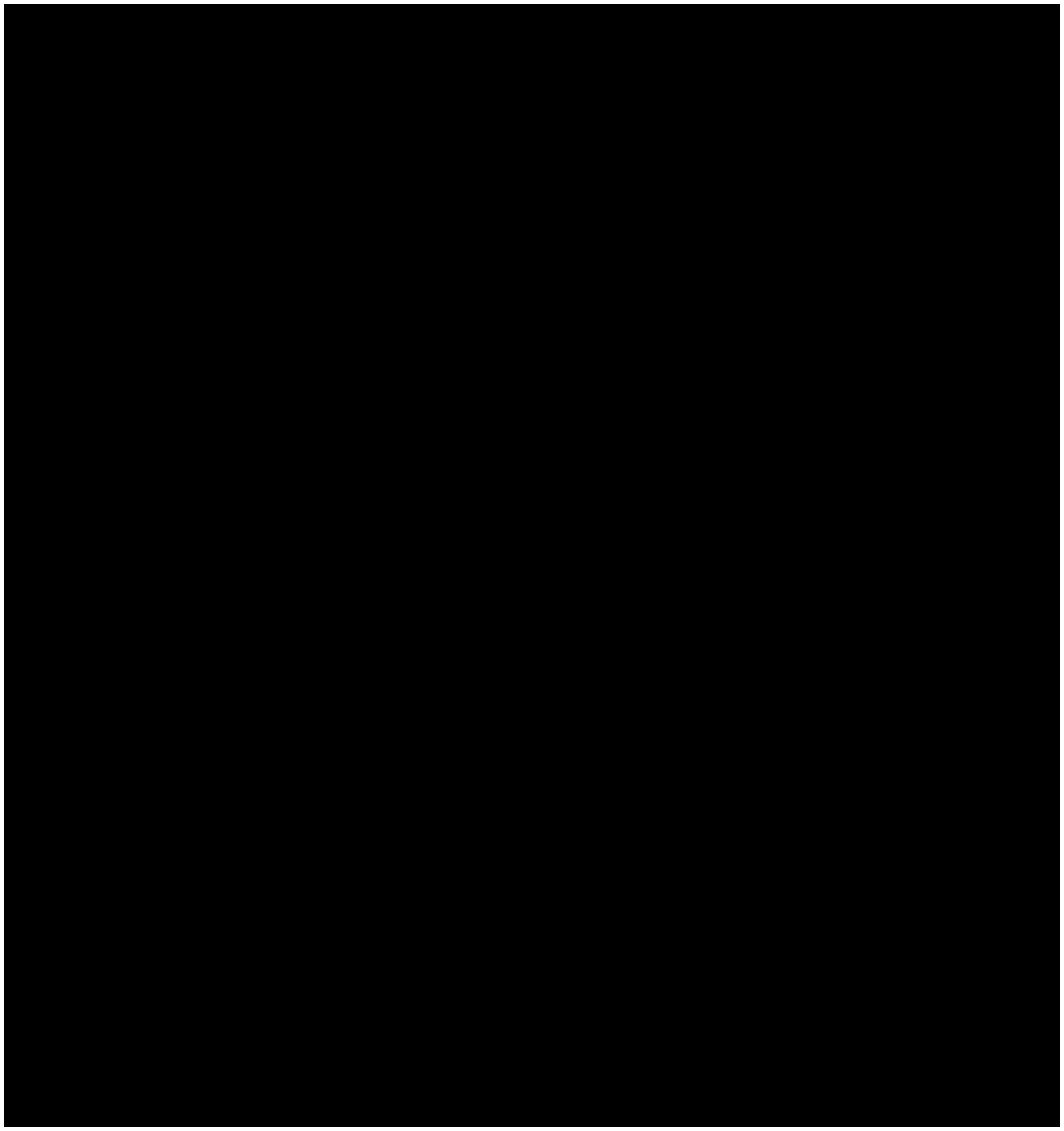

Exhibit D, ANDA excerpt at 37.

NON-INFRINGEMENT OF THE '209 PATENT

64. Infringement of a patent under 35 U.S.C. §271(e)(2) requires a comparison between the patent claims and the ANDA applicant's proposed generic drug. If any claim limitation is absent from the ANDA applicant's proposed generic drug, there is no infringement as a matter of law. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247-48 (Fed. Cir. 2000); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

65. Alembic's ANDA contains a Paragraph IV certification that the manufacture, use or sale of Alembic's generic deferasirox tablets does not and will not infringe the '209 Patent.

66. The '209 Patent contains three independent claims. Claim 1 is directed to, *inter alia*, "[a] tablet for oral administration consisting of 90 mg deferasirox," claim 2 is directed to, *inter alia*, "[a] tablet for oral administration consisting of 180 mg deferasirox," and claim 3 is directed to, *inter alia*, "[a] tablet for oral administration consisting of 360 mg deferasirox[.]"

67. Independent claim 1 reads:

1. A tablet for oral administration consisting of 90 mg deferasirox;

53.61 mg microcrystalline cellulose;

3.65 mg poly vinyl pyrrolidone K-30;

11.34 mg crospovidone;

0.16 mg poloxamer,

0.81 mg fumed silica;

2.43 mg magnesium stearate; and

4.86 mg seal-coat.

68. Claim 1 recites, *inter alia*, "[a] tablet for oral administration consisting of 90 mg deferasirox[.]" Alembic's generic 180 mg deferasirox tablets contain, *inter alia*, 180 mg of deferasirox. Alembic's generic 180 mg deferasirox tablets do not and will not infringe claim 1 of the '209 Patent.

69. Claim 1 also recites "53.61 mg microcrystalline cellulose; 3.65 mg poly vinyl pyrrolidone K-30; 11.34 mg crospovidone; 0.16 mg poloxamer; 0.81 mg fumed silica; 2.43 mg magnesium stearate; and 4.86 mg seal-coat." Alembic's generic 180 mg deferasirox tablets do

not contain the claimed amounts of the recited formulation components (*see* Exhibit D, ANDA excerpt at 37), and therefore Alembic's 180 mg tablets do not and will not infringe claim 1.

70. Independent claim 3 reads:

3. A tablet for oral administration consisting of 360 mg deferasirox;

214.45 mg microcrystalline cellulose;[2]

14.58 mg poly vinyl pyrrolidone K-30;

45.36 mg crospovidone;

0.65 mg poloxamer;

3.24 mg fumed silica;

9.72 mg magnesium stearate; and

19.44 mg seal-coat.

71. Claim 3 recites, *inter alia*, "[a] tablet for oral administration consisting of 360 mg deferasirox[.]" Alembic's generic 180 mg deferasirox tablets contain, *inter alia*, 180 mg of deferasirox. Alembic's generic 180 mg deferasirox tablets do not and will not infringe claim 3 of the '209 Patent.

72. Claim 3 also recites "214.45 mg microcrystalline cellulose; 14.58 mg poly vinyl pyrrolidone K-30; 45.36 mg crospovidone; 0.65 mg poloxamer; 3.24 mg fumed silica; 9.72 mg magnesium stearate; and 19.44 mg seal-coat." Alembic's generic 180 mg deferasirox tablets do not contain the claimed amounts of the recited formulation components (*see* Exhibit D, ANDA excerpt at 37), and therefore Alembic's 180 mg tablets do not and will not infringe claim 3.

73. Independent claim 2 reads:

[2] Claim 3 should be judicially corrected to read "214.45 mg microcrystalline cellulose," rather than "215.45 mg microcrystalline cellulose." *Joint Stipulation and Order, Actavis Elizabeth LLC v. Novartis Pharm. Corp. et al.*, No. 16-604 (D. Del. July 27, 2017), D.I. 59.

2. A tablet for oral administration consisting of 180 mg deferasirox,

107.23 mg microcrystalline cellulose;

7.29 mg poly vinyl pyrrolidone K-30;

22.68 mg crospovidone;

0.32 mg poloxamer;

1.62 mg fumed silica;

4.86 mg magnesium stearate; and

9.72 mg seal-coat.

74. Although containing 180 mg deferasirox, Alembic's 180 mg deferasirox tablets do not contain 107.23 mg of microcrystalline cellulose as recited in claim 2 of the '209 Patent. [redacted]

75. Accordingly, for at least this reason, Alembic's 180 mg deferasirox tablets to not literally infringe claim 2 of the '209 Patent.

76. The '209 Patent discloses that microcrystalline cellulose can be a filler, a disintegrant, and a binder. *See* '209 Patent, col. 5, ll. 25-30, ll. 36-38. The '209 Patent discloses use of other amounts of microcrystalline cellulose besides amounts recited in claims 1-3, but does not claim them. *See* '209 Patent, col. 6, ll. 43-59, Examples 1-5.

77. Accordingly, for at least this reason, Alembic's 180 mg deferasirox tablets do not infringe the '209 Patent under the doctrine of equivalents.

78. Alembic's 180 mg deferasirox tablets do not contain 7.29 mg of poly vinyl pyrrolidone K-30 as recited in claim 2 of the '209 Patent. [redacted]

79. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets do not literally infringe claim 2 of the '209 Patent.

80. The '209 Patent discloses that poly vinyl pyrrolidone K-30 can be a binder. *See* '209 Patent, col. 5, ll. 36-44. The '209 Patent discloses use of other amounts of poly vinyl pyrrolidone K-30 besides the amounts recited in claims 1-3, but does not claim them. *See* '209 Patent, col. 6, ll. 43-59, Examples 1-5.

81. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets do not infringe the '209 Patent under the doctrine of equivalents.

82. Alembic's 180 mg deferasirox tablets do not contain 22.68 mg of crospovidone as recited in claim 2 of the '209 Patent. [redacted]

83. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets do not literally infringe claim 2 of the '209 Patent.

84. The '209 Patent discloses that crospovidone can be a disintegrant. *See* '209 Patent, col. 5, ll. 28-35. The '209 Patent discloses use of other amounts of crospovidone besides the amounts recited in claims 1-3, but does not claim them. *See* '209 Patent, col. 6, ll. 43-59, Examples 1-5.

85. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets do not infringe the '209 Patent under the doctrine of equivalents.

86. Alembic's generic 180 mg deferasirox tablets do not contain 0.32 mg of poloxamer as recited in claim 2 of the '209 Patent. [redacted]

87. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets do not literally infringe claim 2 of the '209 Patent.

88. The '209 Patent discloses that poloxamer can be a surfactant. *See* '209 Patent, col. 5, ll. 45-49. The '209 Patent discloses use of other amounts of poloxamer besides the amounts recited in claims 1-3, but does not claim them. *See* '209 Patent, col. 6, ll. 43-59, Examples 1-5.

89. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets do not infringe the '209 Patent under the doctrine of equivalents.

90. Alembic's 180 mg deferasirox tablets do not contain 1.62 mg of fumed silica as recited in claim 2 of the '209 Patent. [redacted]

91. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets to not literally infringe claim 2 of the '209 Patent.

92. The '209 Patent discloses that fumed silica can be a glidant. *See* '209 Patent, col. 5, ll. 50-53. The '209 Patent discloses use of other amounts of fumed silica besides the amounts recited in claims 1-3, but does not claim them. *See* '209 Patent, col. 6, ll. 43-59, Examples 1-5.

93. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets to not infringe the '209 Patent under the doctrine of equivalents.

94. Alembic's generic 180 mg deferasirox tablets do not contain 4.86 mg of magnesium stearate as recited in claim 2 of the '209 Patent. [redacted]

95. Accordingly, for this additional reason, Alembic's 180 mg deferasirox tablets do not literally infringe claim 2 of the '209 Patent.

96. The ’209 Patent discloses that magnesium stearate can be a lubricant. *See* ’209 Patent, col. 5, ll. 54-64. The ’209 Patent discloses use of other amounts of magnesium stearate besides the amounts recited in claims 1-3, but does not claim them. *See* ’209 Patent, col. 6, ll. 43-59, Examples 1-5.

97. Accordingly, for this additional reason, Alembic’s 180 mg deferasirox tablets do not infringe the ’209 Patent under the doctrine of equivalents.

98. Alembic’s 180 mg deferasirox tablets do not contain 9.72 mg of seal coat as recited in claim 2 of the ’209 Patent. [redacted]

99. Accordingly, for this additional reason, Alembic’s 180 mg deferasirox tablets do not literally infringe claim 2 of the ’209 Patent.

100. The ’209 Patent discloses Opadry coating material. *See* ’209 Patent, col. 5, ll. 5-15, col. 7, ll. 29-32, Examples, 1, 2, and 5. The ’209 Patent discloses use of other amounts of coating material, like Opadry, besides the amounts recited in claims 1-3, but does not claim them. *See* ’209 Patent, col. 7, ll. 29-32.

101. Accordingly, for this additional reason, Alembic’s 180 mg deferasirox tablets do not infringe the ’209 Patent under the doctrine of equivalents.

102. Alembic’s generic 180 mg deferasirox tablets additionally do not and will not infringe any claim of the ’209 Patent under the doctrine of equivalents based on the doctrine of prosecution history estoppel. Issued claims 1, 2 and 3 of the ’209 Patent were originally filed as application claims 26, 28, and 30, respectively. *See* Exhibit E, Preliminary amendment, 39-51. In a January 5, 2015 Interview Summary, the examiner explained that the “Examiner agreed that changing claims 26, 28, and 30 to ‘consisting of’ type claims to exclude the additional

components taught by the prior art would render the claims free of the prior art." Exhibit F, Jan. 21, 2016 Interview Summary, 52-53. The examiner's Notice of Allowability shows that the patent applicant authorized an examiner amendment, which amended the claims as follows:

Claim 26. A tablet for oral administration **[[according to claim 25 comprising]]** **consisting of 90 mg deferasirox;**

[[24.45 mg avicel PH101]] **53.61 mg microcrystalline cellulose;**

[[29.16 mg avicel PH102;]]

3.65 mg poly vinyl pyrrolidone K-30;

11.34 mg crospovidone;

0.16 mg **[[pluronic F68]]** **poloxamer**;

0.81 mg **[[aerosil]]** **fumed silica**;

2.43 mg magnesium stearate; and **[[,]]**

4.86 mg **[[opadry blue coating]]** **seal-coat**.

Claim 28. A tablet for oral administration **[[according to claim 27 comprising]]** **consisting of 180 mg deferasirox;**

[[48.91 mg avicel PH101]] **107.23 mg microcrystalline cellulose**;

[[58.32 mg avicel PH102;]]

7.29 mg poly vinyl pyrrolidone K-30;

22.68 mg crospovidone;

0.32 mg **[[pluronic F68]]** **poloxamer**;

1.62 mg **[[aerosil]]** **fumed silica**;

4.86 mg magnesium stearate; and **[[,]]**

9.72 mg **[[opadry blue coating]]** **seal-coat**.

Claim 30. A tablet for oral administration **[[according to claim 27 comprising]]** **consisting of 360 mg deferasirox;**

[[97.81 mg avicel PH101]] **215.45 mg microcrystalline cellulose;**

[[116.64 mg avicel PH102;]]

14.58 mg poly vinyl pyrrolidone K-30;

45.36 mg crospovidone;

0.65 mg **[[pluronic F68]]** **poloxamer**;

3.24 mg **[[aerosil]]** **fumed silica**;

9.72 mg magnesium stearate; and **[[,]]**

19.44 mg **[[opadry blue coating]]** **seal-coat**.

Exhibit G, Notice of Allowability, 54-59.

103. As the examiner had previously explained in the January 5 interview, amending "claims 26, 28, and 30 to 'consisting of' type claims [would] exclude the additional components taught by the prior art [and] would render the claims free of the prior art." Exhibit F, Jan. 21, 2016 Interview Summary, 52-53. Indeed, the examiner explained in his Reasons for Allowance that "the above amended claims are allowable over the prior art because the picking and choosing of components and amounts from the prior art required to arrive at the instant claims would be too excessive to be considered *prima facie* obvious." Exhibit G, Notice of Allowability, 59.

104. Acquiescing to the examiner's amendment narrowed claims 1-3 to exclude unclaimed amounts of the claimed components, as contained in Alembic's generic deferasirox tablets. The applicant authorized the examiner's amendment to obtain allowance of the claims over the prior art, as the examiner stated in his Reasons for Allowance.

105. The '209 Patent discloses the use of other, unclaimed amounts of the claimed components, and therefore these features were not unforeseeable to the patent applicant at the time the claims were drafted. There is no reason why the claims of the '209 Patent could not

have recited the use of other, unclaimed amounts. And Novartis cannot argue that the examiner's amendment did not surrender the use of other, unclaimed amounts because the examiner said the amendment would "exclude the additional components taught by the prior art" and then subsequently allowed the claims.

106. Claims 1-3 as issued recite a "tablet for oral administration *consisting of*…" There is an "exceptionally strong presumption that a claim term set off with 'consisting of' is closed to unrecited elements." *Multilayer Stretch Cling Film Holdings, Inc.*, 831 F.3d at 1359. Novartis cannot overcome the presumption that "consisting of" is closed because the examiner said changing the claims to "consisting of" type claims would "exclude the additional components taught by the prior art" and then subsequently allowed the claims.

107. As described above, Alembic's 180 mg deferasirox tablets contain unclaimed amounts of each of the claimed components. Alembic's 180 mg deferasirox tablets also contain unclaimed components, [redacted]. *See* Exhibit D, ANDA excerpt at 37.

108. Accordingly, Alembic's 180 mg deferasirox tablets cannot infringe any claim of the '209 Patent under the doctrine of equivalents.

COUNT I

DECLARATORY JUDGMENT OF NON-INFRINGEMENT OF ALEMBIC'S GENERIC 180 MG DEFERASIROX TABLETS

109. Alembic hereby incorporates by reference its allegations contained in paragraphs 1 through 108 of this Complaint as though fully set forth herein.

110. This claim arises under the Patent Laws of the United States, 35 U.S.C. §1 et seq., the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, and the Hatch-Waxman Act, 21 U.S.C. §355(j)(5)(C).

111. Novartis caused the ’209 Patent to be listed in the Orange Book as covering its Jadenu® 180 mg tablets.

112. Alembic filed an ANDA with a Paragraph IV certification stating the ’209 Patent is not and will not be infringed by the marketing of Alembic’s 180 mg deferasirox tablets.

113. Alembic intends to sell its generic 180 mg deferasirox tablets, as described in ANDA No. 211824, once it obtains final FDA approval, which is currently blocked by a first-filer’s 180-day exclusivity.

114. There is a real, actual and continuing justiciable case and controversy between Alembic and Novartis regarding the infringement of the ’209 Patent by Alembic’s generic 180 mg deferasirox tablets.

115. The ’209 Patent will not be infringed by the manufacture, use, offer for sale, sale, and/or importation of Alembic’s generic 180 mg deferasirox tablets for which Alembic has submitted ANDA No. 211824.

116. Accordingly, Alembic seeks and is entitled to a judicial declaration that the manufacture, use, offer for sale, sale, and/or importation of Alembic’s 180 mg deferasirox tablets, described in ANDA No. 211824, do not and will not infringe, directly or indirectly, any valid claim of the ’209 Patent.

PRAYER FOR RELIEF

WHEREFORE, Alembic prays for a declaratory judgment against Novartis as follows:

A. Judgment against Novartis declaring that the ’209 Patent is not and will not be infringed by Alembic’s 180 mg deferasirox tablets as described in ANDA No. 211824;

B. Declaring the manufacture, marketing, use, offer for sale, sale, and/or importation of Alembic’s generic 180 mg deferasirox tablets do not infringe and will not, if marketed, infringe or induce or contribute to the infringement of any valid claim of the ’209 Patent;

C. Awarding Alembic its costs, expenses and reasonable attorneys' fees pursuant to 35 U.S.C. §285; and

D. Awarding Alembic such other and further relief as the Court deems just and reasonable.

Dated: November 27, 2019

By: /s/ Lisa J. Rodriguez

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Facsimile: 201-489-0495

Attorneys for Plaintiff
Alembic Pharmaceuticals Ltd.

CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 11.2

Pursuant to Local Civil Rule 11.2, the undersigned hereby certifies that the patent at issue in this action, U.S. Patent No. 9,283,209, is the subject of the following actions pending before this Court:

Piramal Healthcare UK Ltd. v. Novartis Pharm. Corp, et al., Case No. 2:19-cv-12651

Cipla Ltd. v. Novartis AG, et al., Case No. Pending

The undersigned further certifies that the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: November 27, 2019

By: /s/ Lisa J. Rodriguez
Lisa J. Rodriguez

CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 201.1

Pursuant to Local Civil Rule 201.1, the undersigned hereby certifies that this action involves complex legal issues and the legal issues predominate over the factual issues; therefore, the matter is not appropriate for compulsory arbitration.

Dated: November 27, 2019

By: /s/ Lisa J. Rodriguez
Lisa J. Rodriguez

Exhibit A

US009283209B2

(12) **United States Patent**
Ghosh et al.

(10) **Patent No.: US 9,283,209 B2**
(45) **Date of Patent: Mar. 15, 2016**

(54) **ORAL FORMULATIONS OF DEFERASIROX**

(71) Applicants: **Indrajit Ghosh**, Hillsborough, NJ (US); **Jia-Ai Zhang**, Skillman, NJ (US)

(72) Inventors: **Indrajit Ghosh**, Hillsborough, NJ (US); **Jia-Ai Zhang**, Skillman, NJ (US)

(73) Assignee: **NOVARTIS AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 260 days.

(21) Appl. No.: **14/198,872**

(22) Filed: **Mar. 6, 2014**

(65) **Prior Publication Data**

US 2015/0017241 A1 Jan. 15, 2015

Related U.S. Application Data

(60) Provisional application No. 61/774,893, filed on Mar. 8, 2013, provisional application No. 61/824,435, filed on May 17, 2013.

(51) **Int. Cl.**

A61K 31/41	(2006.01)
A61K 9/22	(2006.01)
A61K 31/4196	(2006.01)
A61K 9/20	(2006.01)
A61K 9/28	(2006.01)
A61K 9/50	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/4196*** (2013.01); ***A61K 9/2031*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 9/2077*** (2013.01); ***A61K 9/2095*** (2013.01); ***A61K 9/2846*** (2013.01); ***A61K 9/2886*** (2013.01); ***A61K 9/2893*** (2013.01); ***A61K 9/5026*** (2013.01); ***A61K 9/5089*** (2013.01)

(58) **Field of Classification Search**

USPC 514/383; 424/468

See application file for complete search history.

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO97/49395 A1	12/1997
WO	WO2005/097062 A1	10/2005
WO	WO2009130604 A2	10/2009
WO	WO2010/143006 A1	12/2010

Primary Examiner — Adam C Milligan

(74) *Attorney, Agent, or Firm* — Eckert Seamans Cherin & Mellott, LLC

(57) **ABSTRACT**

Orally administerable deferasirox formulations are disclosed having reduced release under gastric conditions and fast release at near neutral pH or at neutral pH.

3 Claims, 13 Drawing Sheets

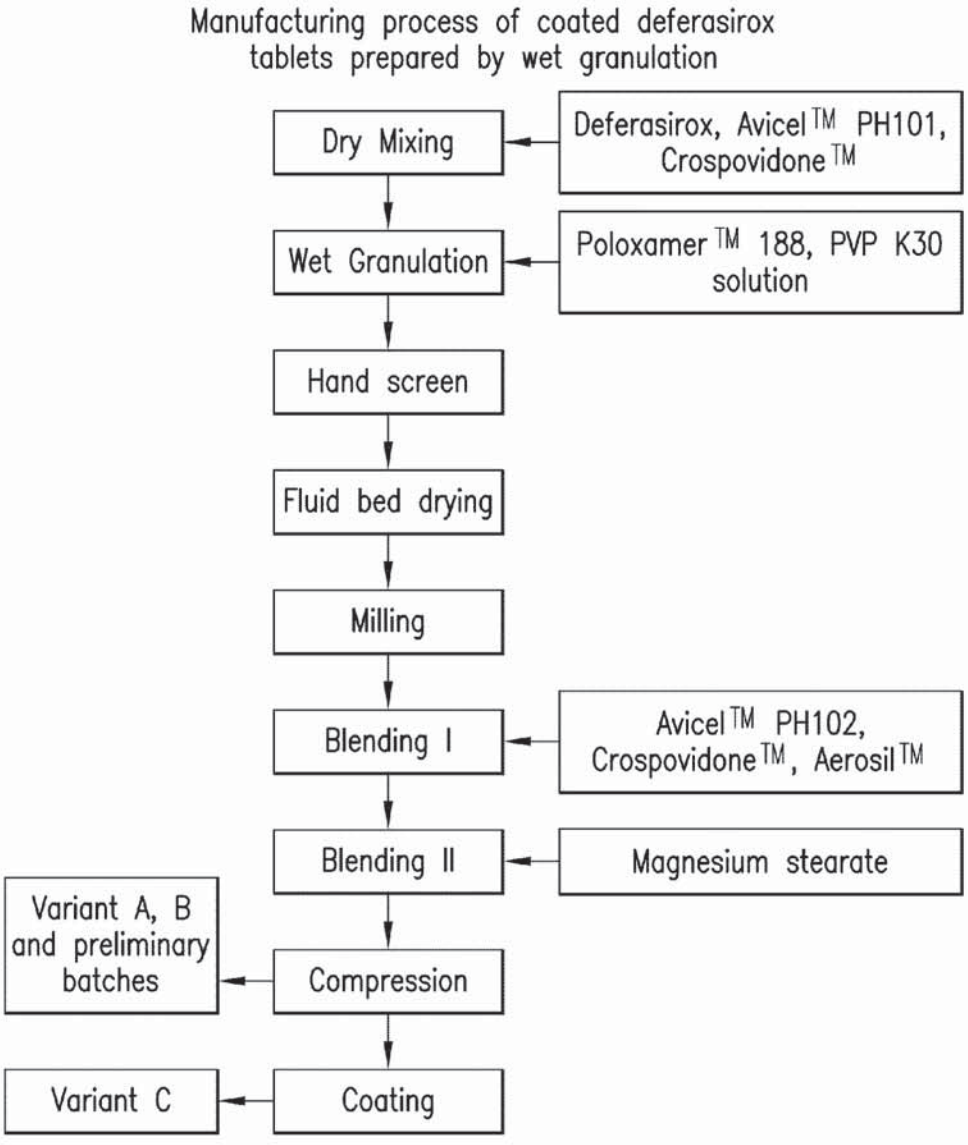

Manufacturing process of coated deferasirox tablets prepared by wet granulation
Dry Mixing
Deferasirox, Avicel™ PH101, Crospovidone™
Wet Granulation
Poloxamer™ 188, PVP K30 solution
Hand screen
Fluid bed drying
Milling
Blending I
Avicel™ PH102, Crospovidone™, Aerosil™
Blending II
Magnesium stearate
Compression
Variant A, B and preliminary batches
Coating
Variant C

FIG. 1

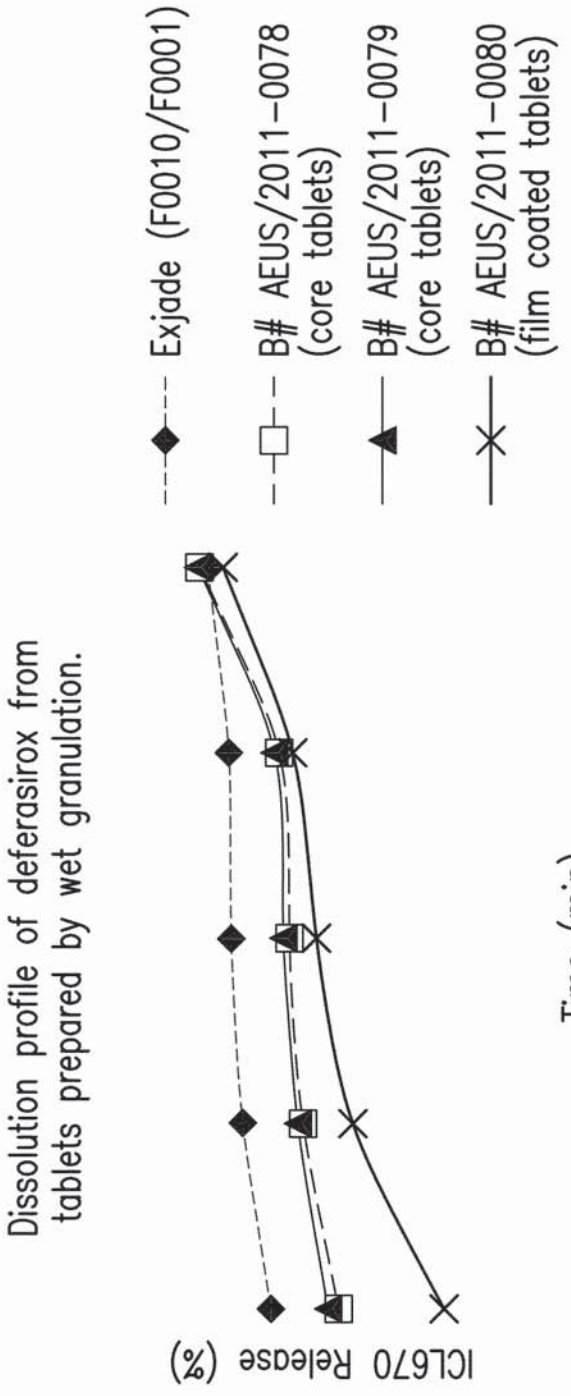

Dissolution profile of deferasirox from tablets prepared by wet granulation.
ICL670 Release (%)
Time (min)
Exjade (F0010/F0001)
B# AEUS/2011-0078 (core tablets)
B# AEUS/2011-0079 (core tablets)
B# AEUS/2011-0080 (film coated tablets)

FIG. 2

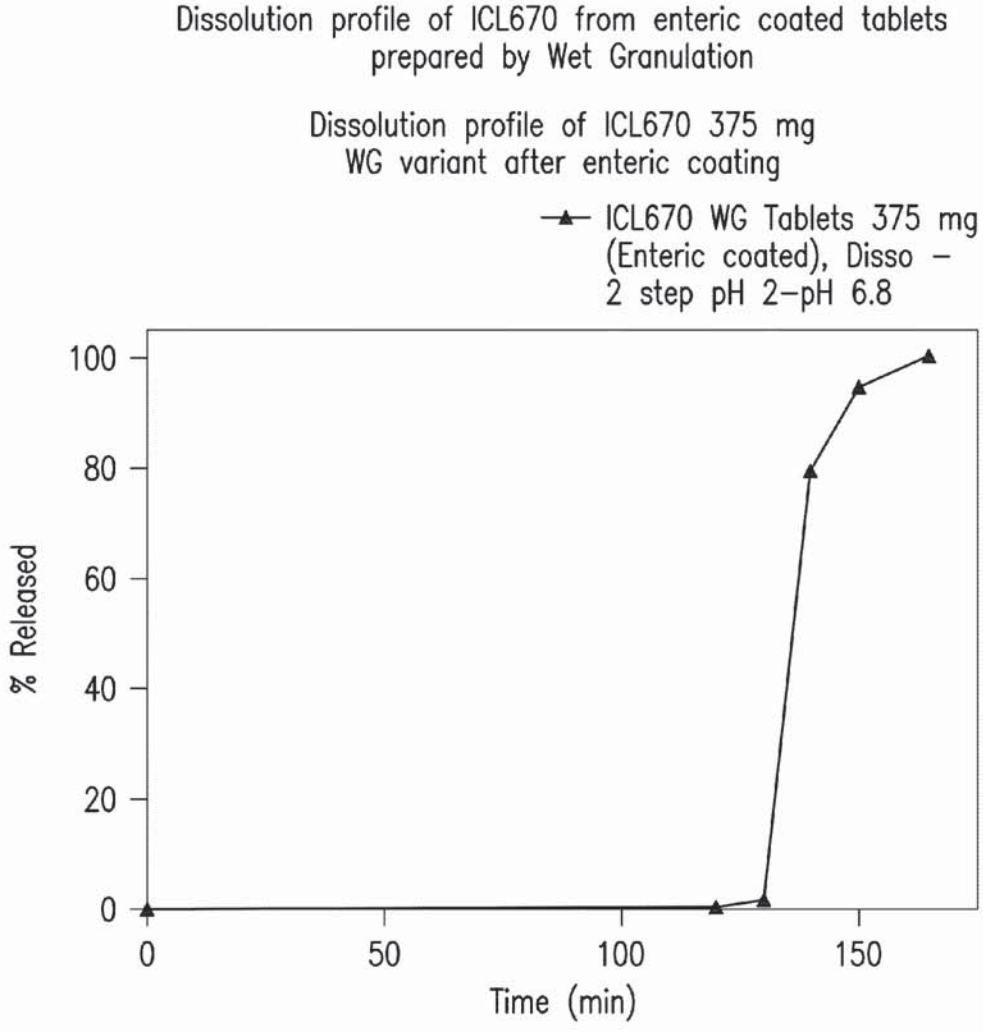

Dissolution profile of ICL670 from enteric coated tablets prepared by Wet Granulation
Dissolution profile of ICL670 375 mg WG variant after enteric coating
ICL670 WG Tablets 375 mg (Enteric coated), Disso – 2 step pH 2–pH 6.8
% Released
100
80
60
40
20
0
0
50
100
150
Time (min)

FIG.3

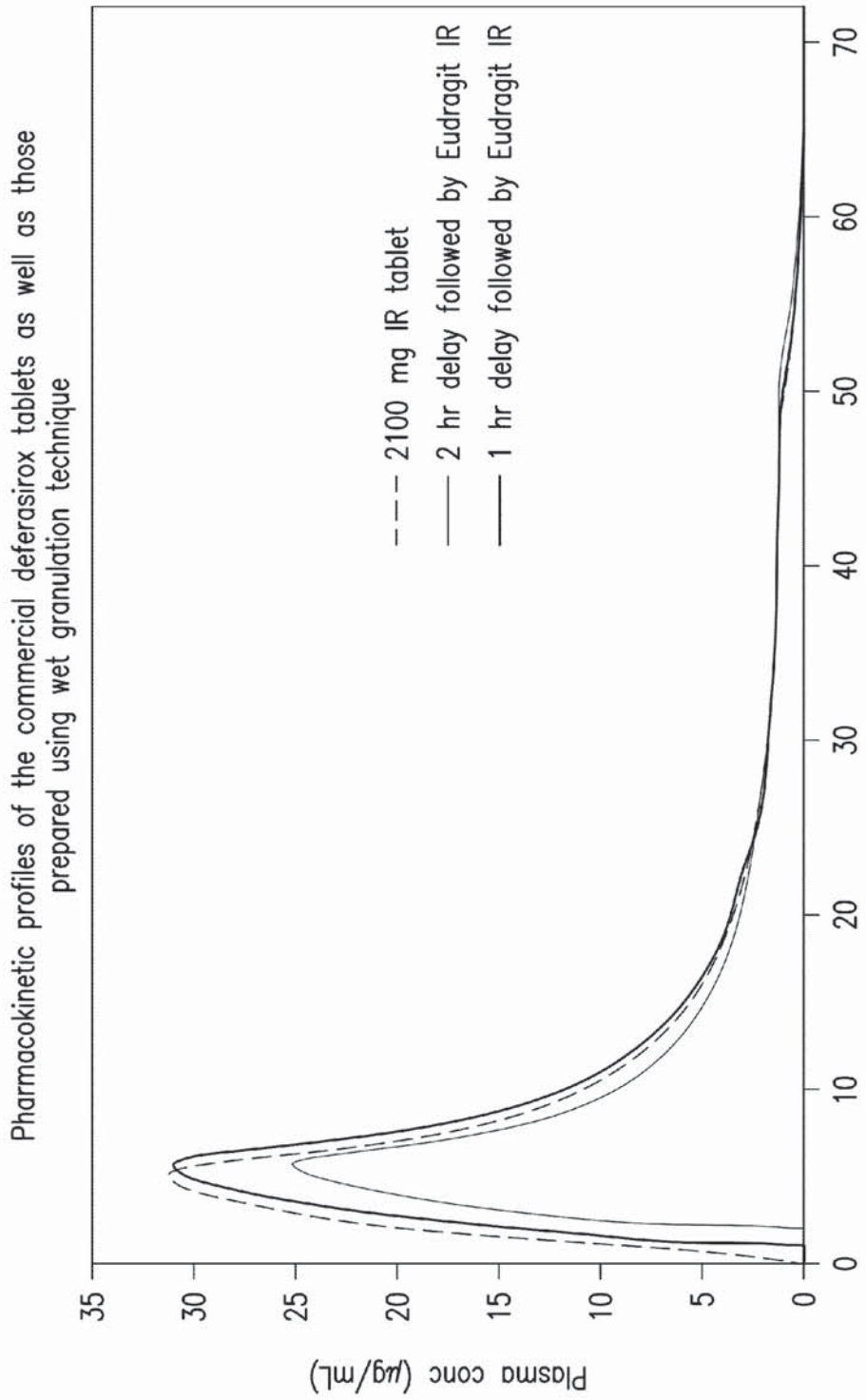

Pharmacokinetic profiles of the commercial deferasirox tablets as well as those prepared using wet granulation technique
2100 mg IR tablet
2 hr delay followed by Eudragit IR
1 hr delay followed by Eudragit IR
Plasma conc (μg/mL)
Time (hr)
0
5
10
15
20
25
30
35
0
10
20
30
40
50
60
70

FIG.4

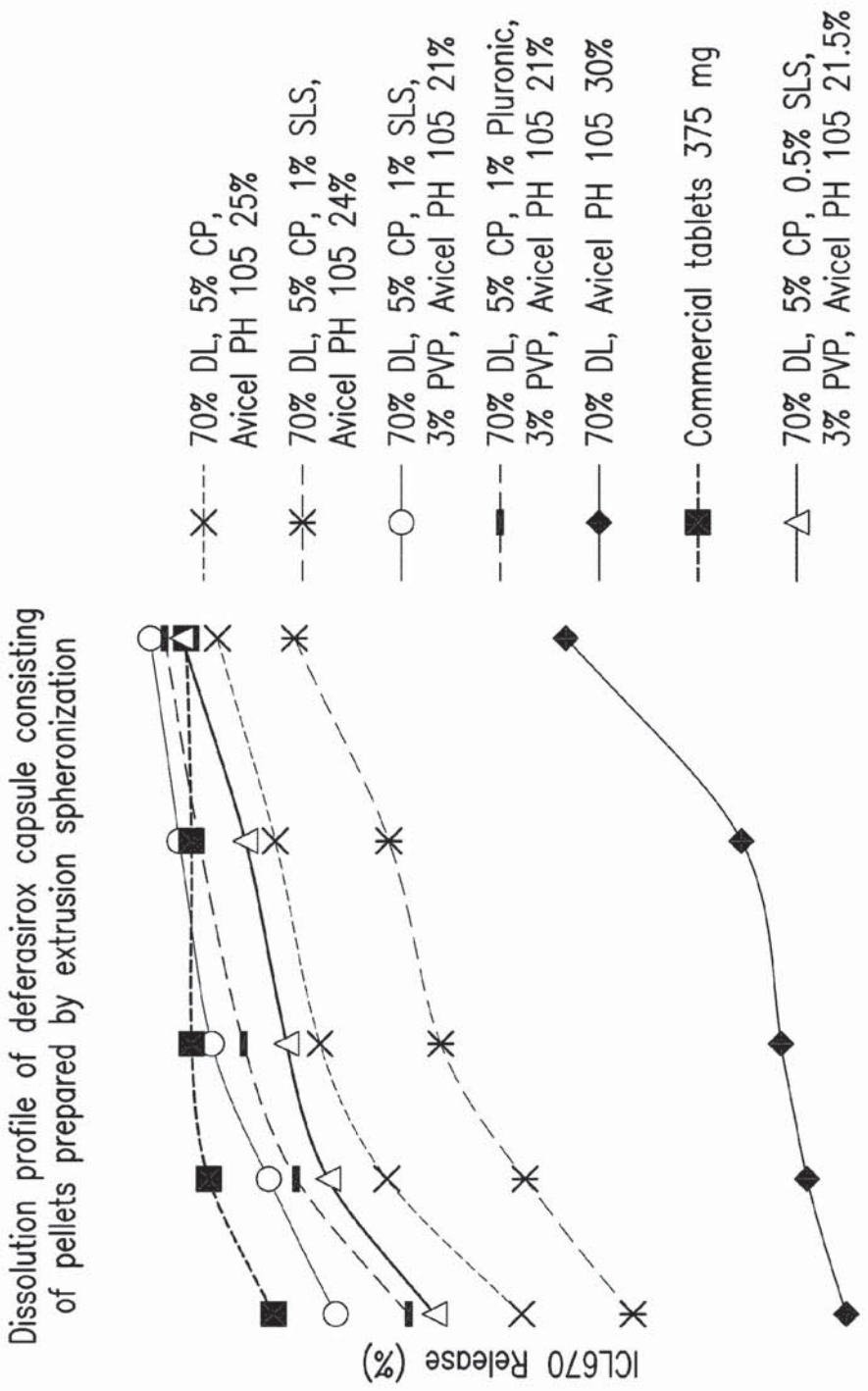

Dissolution profile of deferasirox capsule consisting of pellets prepared by extrusion spheronization
ICL670 Release (%)
Time (min)
70% DL, 5% CP, Avicel PH 105 25%
70% DL, 5% CP, 1% SLS, Avicel PH 105 24%
70% DL, 5% CP, 1% SLS, 3% PVP, Avicel PH 105 21%
70% DL, 5% CP, 1% Pluronic, 3% PVP, Avicel PH 105 21%
70% DL, Avicel PH 105 30%
Commercial tablets 375 mg
70% DL, 5% CP, 0.5% SLS, 3% PVP, Avicel PH 105 21.5%

FIG.5

Dissolution profile of deferasirox capsules consisting of enteric coated pellets prepared by extrusion spheronization.

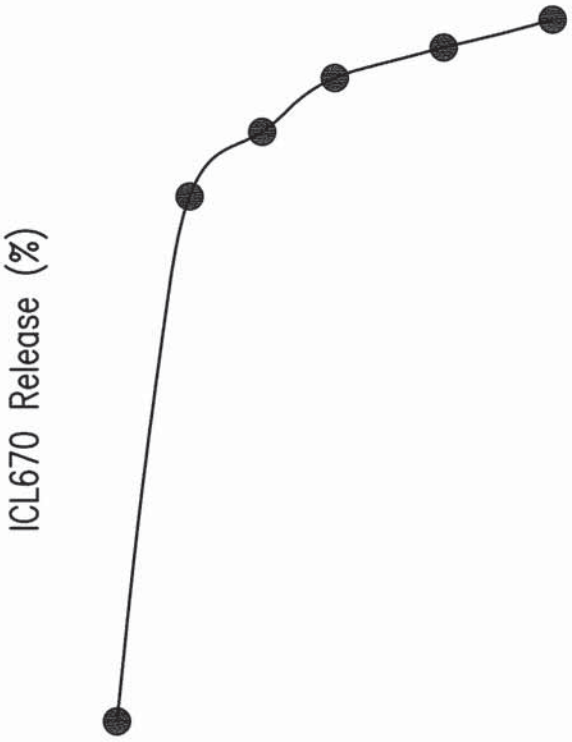


FIG.6

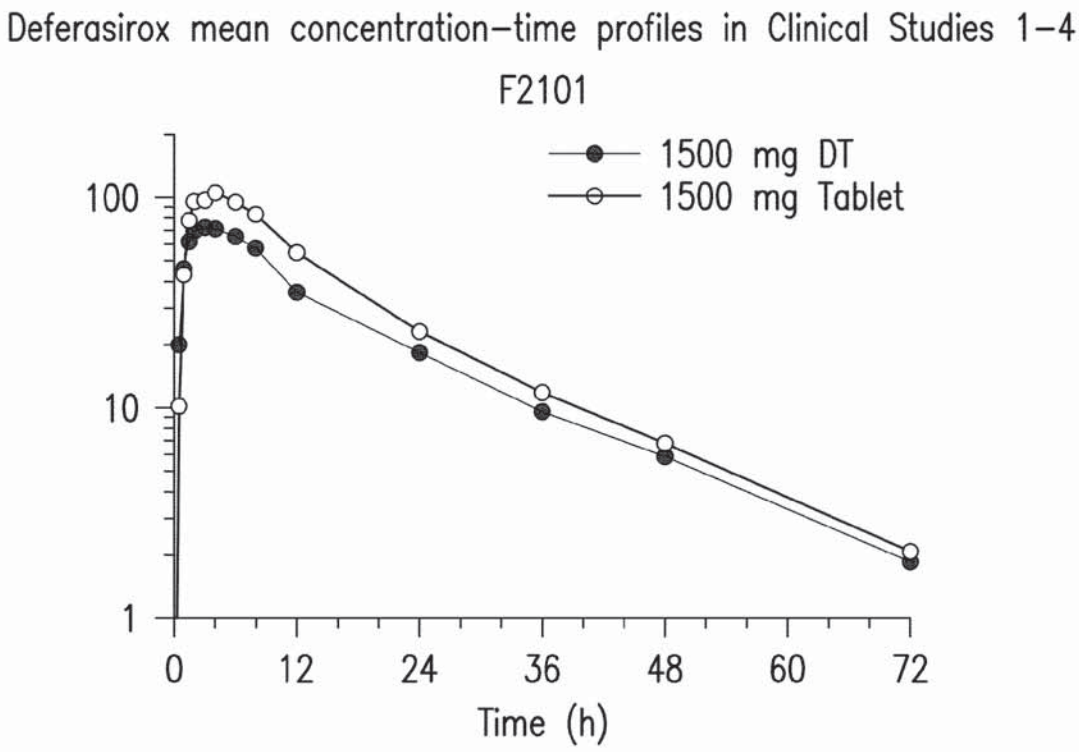

Deferasirox mean concentration–time profiles in Clinical Studies 1–4
F2101
1500 mg DT
1500 mg Tablet
100
10
1
0
12
24
36
48
60
72
Time (h)

FIG. 7A

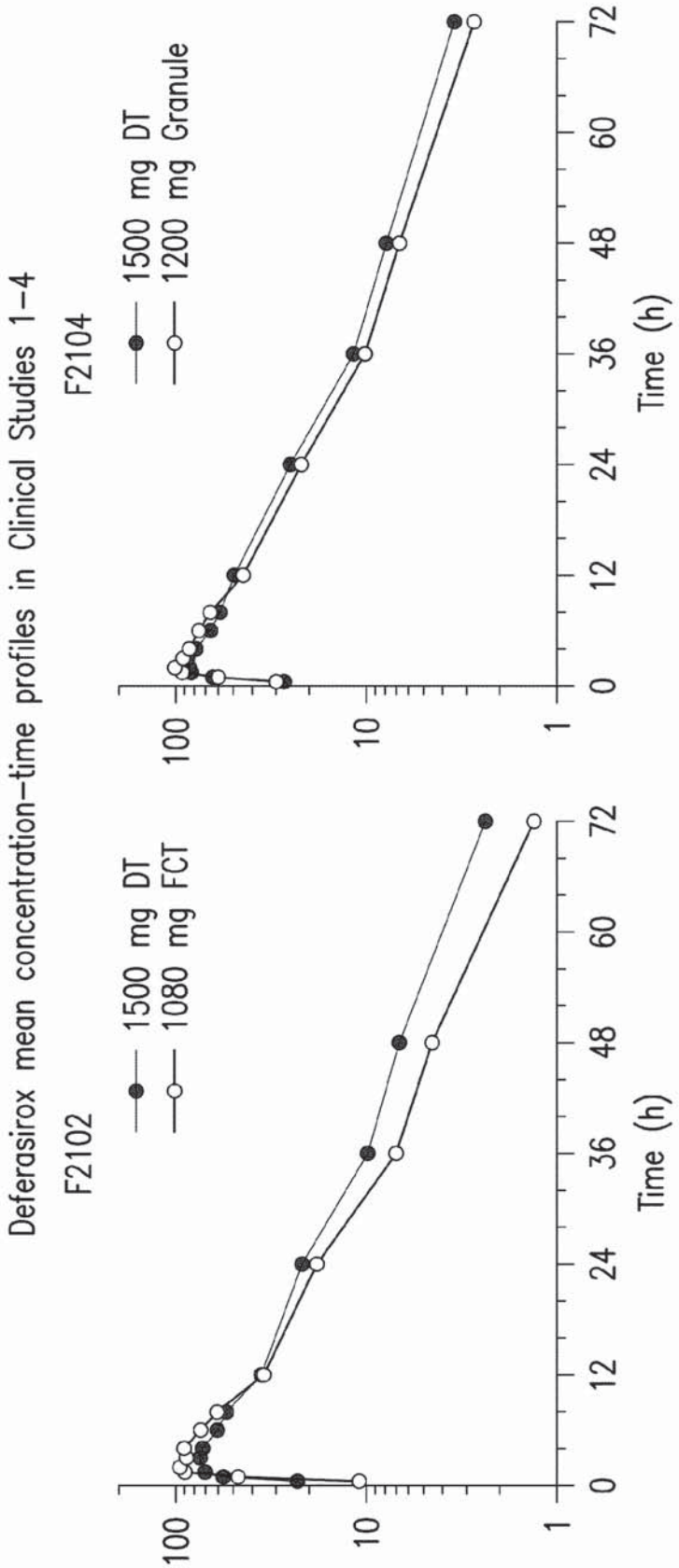

Deferasirox mean concentration–time profiles in Clinical Studies 1–4
F2102
1500 mg DT
1080 mg FCT
F2104
1500 mg DT
1200 mg Granule
100
10
1
0
12
24
36
48
60
72
Time (h)

FIG. 7B

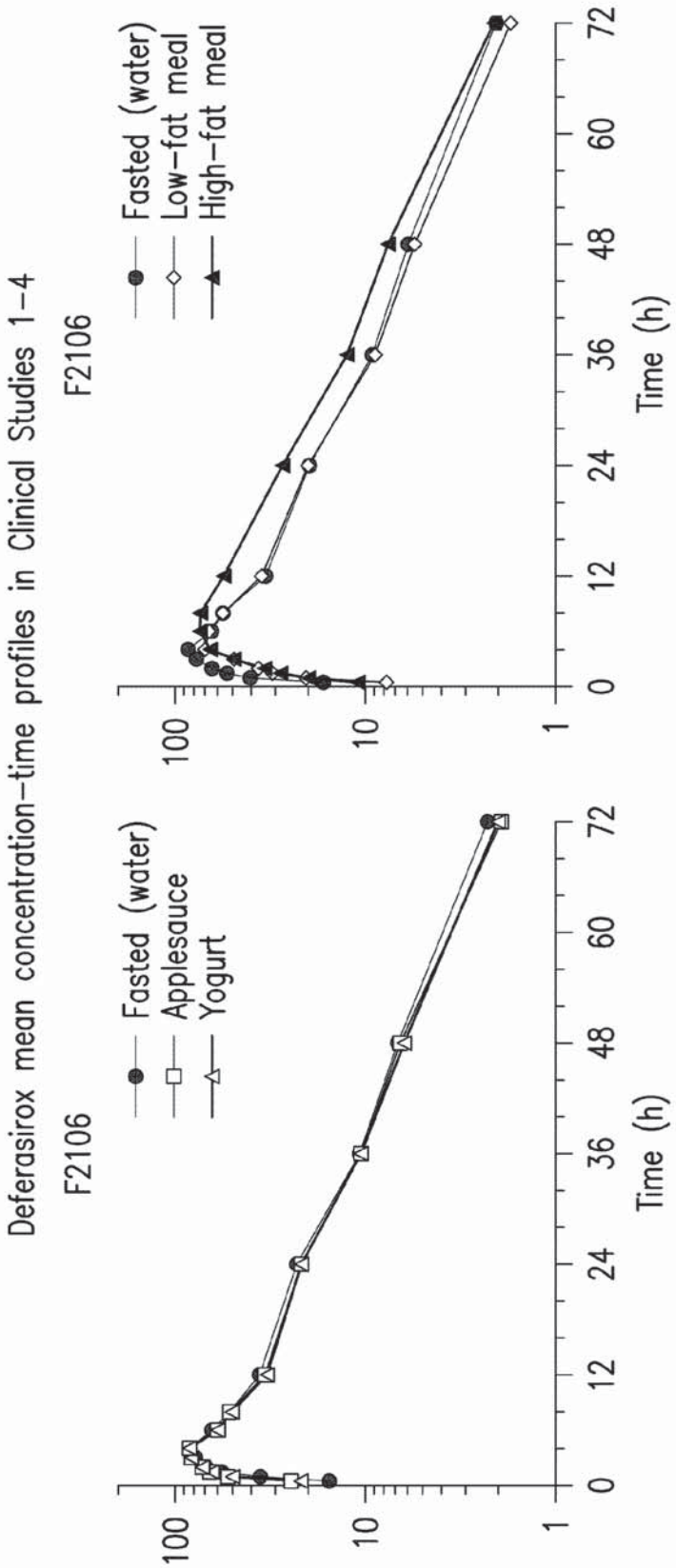

Deferasirox mean concentration–time profiles in Clinical Studies 1–4
F2106
Fasted (water)
Low–fat meal
High–fat meal
100
10
1
0
12
24
36
48
60
72
Time (h)
F2106
Fasted (water)
Applesauce
Yogurt
100
10
1
0
12
24
36
48
60
72
Time (h)

FIG. 7C

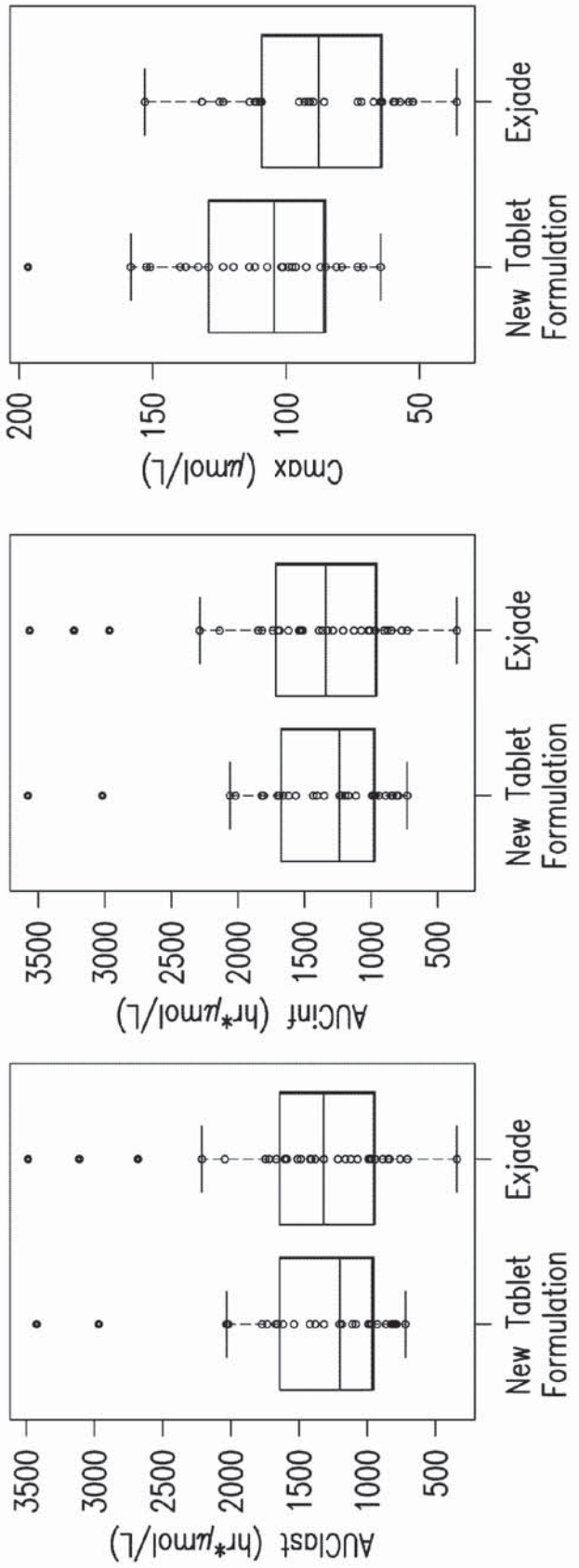

Cmax (μmol/L)
200
150
100
50
New Tablet Formulation
Exjade
AUCinf (hr*μmol/L)
3500
3000
2500
2000
1500
1000
500
New Tablet Formulation
Exjade
AUClast (hr*μmol/L)
3500
3000
2500
2000
1500
1000
500
New Tablet Formulation
Exjade

FIG.8

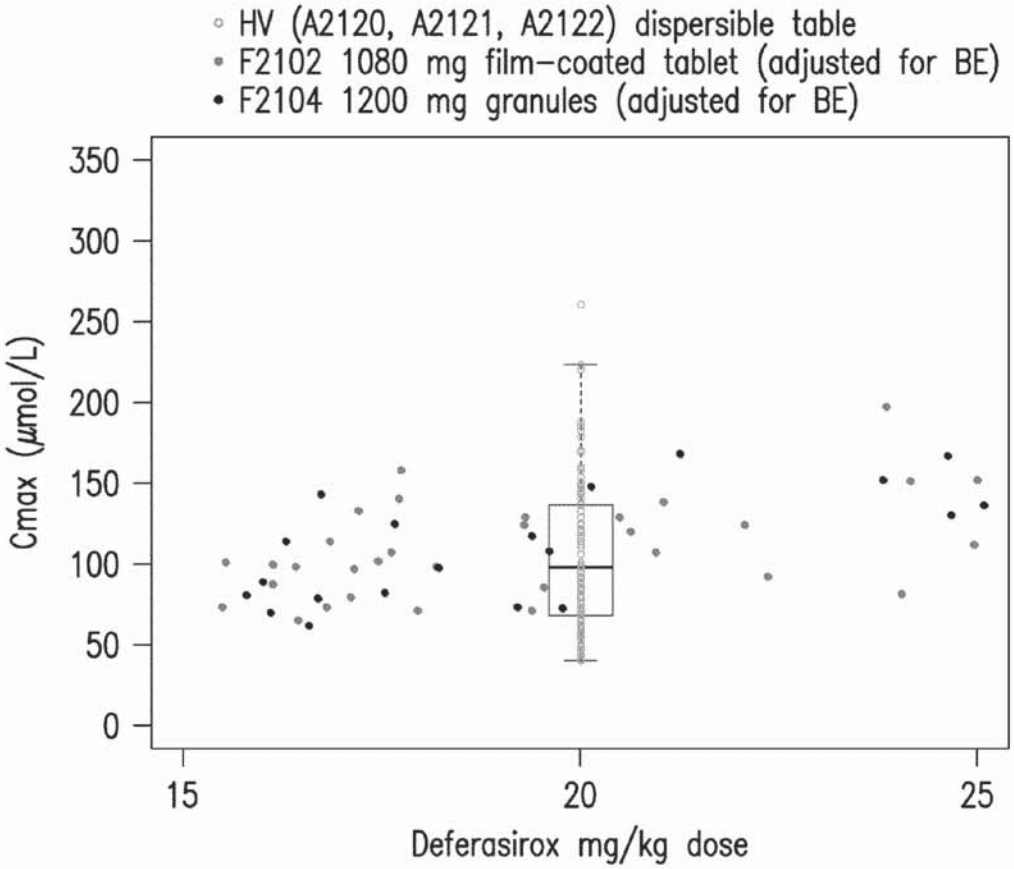

HV (A2120, A2121, A2122) dispersible table
F2102 1080 mg film-coated tablet (adjusted for BE)
F2104 1200 mg granules (adjusted for BE)
Cmax (µmol/L)
350
300
250
200
150
100
50
0
15
20
25
Deferasirox mg/kg dose

FIG.9

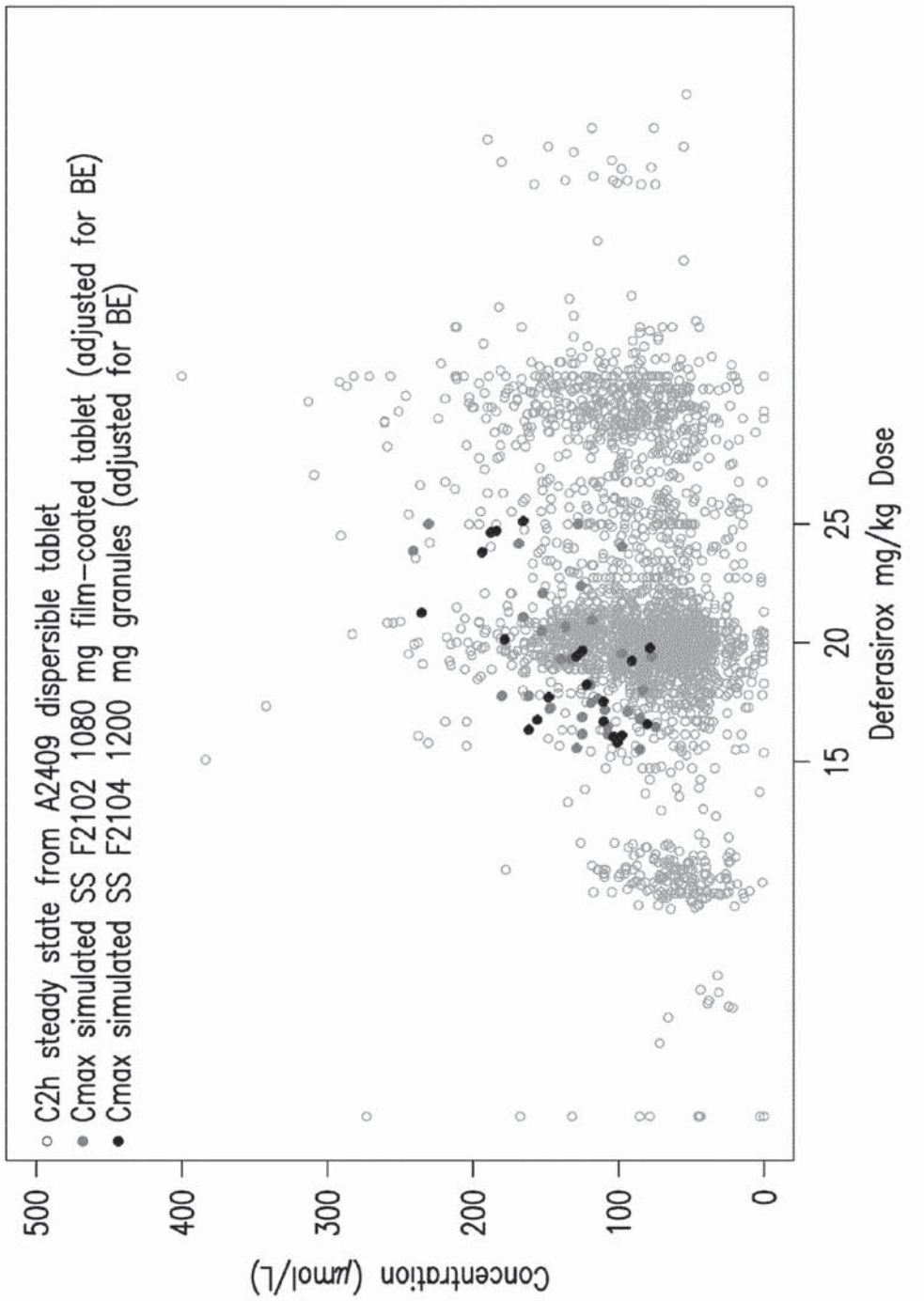

C2h steady state from A2409 dispersible tablet
Cmax simulated SS F2102 1080 mg film-coated tablet (adjusted for BE)
Cmax simulated SS F2104 1200 mg granules (adjusted for BE)
Concentration (μmol/L)
0
100
200
300
400
500
15
20
25
Deferasirox mg/kg Dose

FIG. 10

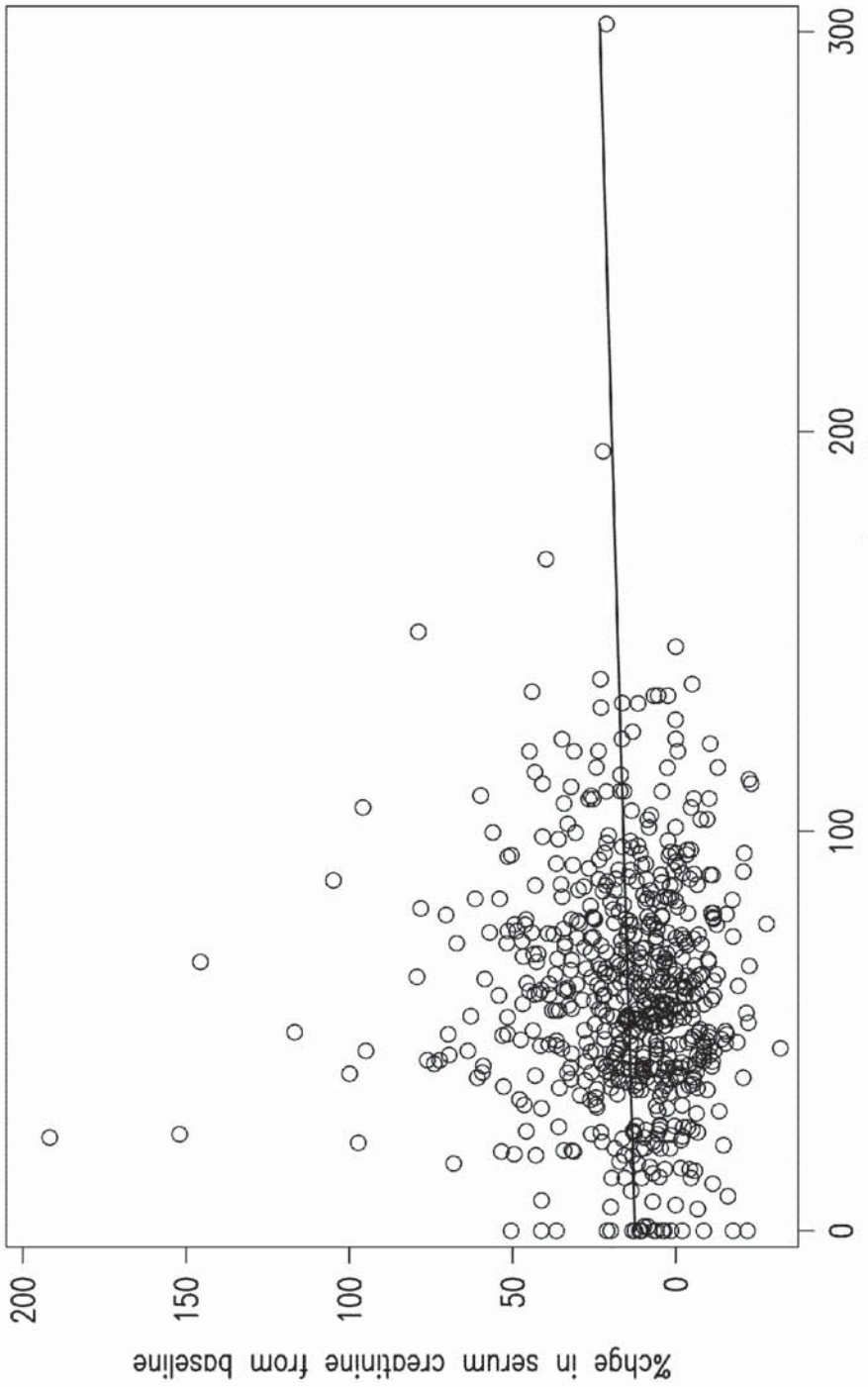

%chge in serum creatinine from baseline
200
150
100
50
0
0
100
200
300
C2h after 1st dose (μmol/L)
Regression

FIG. 11

ORAL FORMULATIONS OF DEFERASIROX

FIELD OF THE INVENTION

Compositions and technologies of manufacturing medicaments for Exjade™ (desferasirox) with high drug loading to potentially reduce variability of the gastric emptying, minimize food effect, prevent gastric irritation and also reduce the size and delivery route of the dosage form to improve patient compliance.

BACKGROUND OF THE INVENTION

Exjade™ (deferasirox) is a marketed product from Novartis that is formulated as dispersible tablets in 125 mg, 250 mg and 500 mg dose strengths. Exjade™ (deferasirox) is given once daily for the treatment of chronic iron overload due to blood transfusions, which is referred to by medical professionals and clinicians as transfusional hemosiderosis, in patients 2 years of age and older.

Due to the poor solubility of Exjade™ (deferasirox), a high dose is required to achieve the desired therapeutic effect, which results in unwanted side effects, such as gastrointestinal (GI) irritation and kidney toxicity. The poor solubility of Exjade™ (deferasirox) also presents technical difficulties in developing pharmaceutical formulations, as seen from the solubility profile summarized in Table 1. To meet the high dose requirement and reduce pill burden Exjade™ (deferasirox) was developed as dispersible tablets with about 29.4% drug load. The disadvantage of this type of formulation is that the tablets have to be dispersed in water or appropriate liquid, such as in orange juice or apple juice and stirred until a fine suspension is obtained prior to administration. Further, the dispersible tablets have to be taken at least 30 minutes before food.

TABLE 1

Exjade ™ (deferasirox) Solubility Profile

pH	Solubility (mg/ml) at 37 C.
water	0.02
1	<0.01
2	<0.01
3	<0.01
4	<0.01
5	<0.01
7.5	0.167

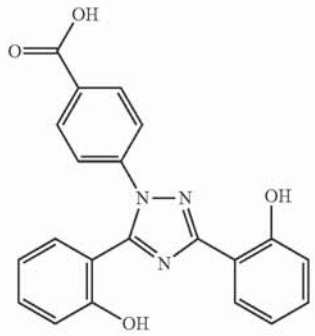
Gastrointestinal (GI) irritation has been reported for patients using the current dispersible tablets. Upper gastrointestinal ulceration and hemorrhage has also been reported in patients, including children and adolescents. Multiple ulcers have been observed in some patients. Stomach bleeding is a severe side effect that occurs for patients currently under Exjade therapy because of acidity of Exjade™ (deferasirox), and local accumulation of drug content. Therefore, it is desirable to re-formulate an Exjade™ (deferasirox) dispersible formulation to limit the direct contact of drug compound with stomach mucosa. It is further desirable to provide a high load deferasirox formulation that has no food effect. For instance, as enteric coated form or multi-particulate form where dosage form is emptied faster from the stomach. In addition, data from THALASSA (NTDT) study placebo arms (contains all components in Exjade™ dispersible tablets (except API) suggest that excipients in the marketed dispersible formulation could contribute to GI adverse effects (AE) profile of Exjade™.

The current invention describes formulated compositions and the corresponding technology of manufacturing tablets for Exjade™ (deferasirox) to prevent gastrointestinal irritation, having no food effect and improve patient compliance.

With aforementioned cumbersome in drug administration, it is also desirable to re-formulate the current dispersible Exjade™ (deferasirox) tablets into swallowable (ingestable, orally administerable) tablets and sachets, which increase the drug load by up to and greater than 100% of the current dispersible tablet and sachet per dose requiring less pill burden while maintaining equivalent pharmacokinetic profile, and consequently the therapeutic outcome as compared to commercially marketed dispersible Exjade™ (deferasirox) tablets.

SUMMARY OF THE INVENTION

An aspect of the present invention provides a tablet for treating diseases which cause an excess of metal, such as iron, in a human or animal body or are caused by an excess of metal in a human comprising Exjade™ (deferasirox) of the formula I:



or a pharmaceutically acceptable salt thereof present in an amount of from 45% to 60% by weight based on the total weight of the tablet, said tablet having a reduced release under gastric conditions and fast release at near neutral pH or at neutral pH.

Typically, a drug product that shows faster dissolution will have a much higher exposure level when tested in humans. Surprisingly, in the current case. Exjade™ (deferasirox) tablets formulated to have slower release showed much higher bioavailability and no food effects when compared with commercial dispersible tablets, which have a faster dissolution rate but which exhibit significantly lower exposure levels. The characteristics of the new swallowable (ingestable, orally administerable) tablets and sachets, such as its disintegration time and dissolution are uniquely needed to reach the intended exposure levels.

Another aspect of the present invention provides a coated tablet comprising (a) deferasirox or a pharmaceutically acceptable salt thereof, and (b) at least one pharmaceutically acceptable excipient suitable for the preparation of tablets, wherein deferasirox or a pharmaceutically acceptable salt thereof is present in an amount of from 45% to 60% by weight based on the total weight of the tablet. The tablets are optionally enteric coated.

Another aspect of the present invention provides a sachet comprising (a) deferasirox or a pharmaceutically acceptable salt thereof, and (b) at least one pharmaceutically acceptable excipient suitable for the preparation of sachets, wherein

deferasirox or a pharmaceutically acceptable salt thereof is present in an amount of from 45% to 60% by weight based on the total weight of the sachet.

Another aspect of the present invention provides a coated deferasirox tablet comprising:

(i) at least one filler in an amount of about to 10% to 40% by weight based on the total weight of the tablet;

(ii) at least one disintegrant in an amount of about 1% to 10% in weight based on the total weight of the tablet:

(iii) at least one binder in an amount of about 1% to 5% by weight based on the total weight of the tablet;

(iv) at least one surfactant in an amount of about 0.0% to 2% by weight based on the total weight of the tablet;

(v) at least one glidant in an amount of about 0.1% to 1% by weight based on the total weight of the tablet;

(vi) at least one lubricant in an amount of less than about 0.1% to 2% % by weight based on the total weight of the tablet; and

(vii) a coating.

Another aspect of the present invention provides a process for the preparation of a coated deferasirox tablet according to any one of the preceding claims, which process comprises

(i) mixing deferasirox or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient;

(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator followed by drying and screening to produce a granulate;

(iii) mixing the granulates obtained in step (ii) with at least one pharmaceutically acceptable excipient to form a mixture;

(iv) compressing the mixture obtained in step (iii) to form a tablet; and

(v) coating the tablet.

Yet another aspect of the present invention provides a process for the preparation of a coated deferasirox tablet, comprising the steps of:

(i) mixing deferasirox or a pharmaceutically acceptable salt and at least one pharmaceutically acceptable excipient;

(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator;

(iii) extruding and spheronizing the wet granulates obtained in step (ii);

(iv) drying the extruded and spheronized pellets; and

(v) coating the pellets.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts a flow chart showing the manufacturing process of coated deferasirox tablets prepared by wet granulation

FIG. **2** summarizes the dissolution profile of deferasirox from tablets prepared by wet granulation

FIG. **3** summarizes the dissolution profile of deferasirox from enteric coated tablets prepared by wet granulation.

FIG. **4** summarizes the actual pharmacokinetic profiles of the commercial deferasirox tablets as well as those prepared using wet granulation technique

FIG. **5** summarizes the dissolution profile of deferasirox capsule consisting of pellets prepared by extrusion spheronization.

FIG. **6** summarizes the dissolution profile of deferasirox capsules consisting of enteric coated pellets prepared by extrusion spheronization.

FIG. **7**A, FIG. **7**B, and FIG. **7**C summarizes deferasirox mean concentration versus time profiles for the invented formulations.

FIG. **8** summarizes inter-subject varabilities in pharmokinetic parameters AUC_{last}, AUC_{inf}, and C_{max} for the invented formulations.

FIG. **9** summarizes a deferasirox C_{max} comparison in the invented formulation versus commercially available formulation for healthy volunteers.

FIG. **10** summarizes steady state deferasirox C2h values versus Cmax for the invented formulation versus commercially available formulation.

FIG. **11** summarizes a scatterplot of deferasirox C2h for the invented formulation on Day 1 versus percent change from baseline in serum creatinine at Week 4.

DETAILED DESCRIPTION OF THE INVENTION

The current commercial formulation of Exjade™ (deferasirox) is a dispersible tablet. The current formulation is dosed under fasted state due to a GI irritation issue. The new intended swallowable (ingestable, orally administerable) deferasirox tablets have an improved GI irritation AE profile due to a slower release profile and removal of sodium lauryl sulfate and lactose from the dispersible formulation. The invented formulation allows for patient compliance, no food effects and reduced GI irritation as compared to the current marketed Exjade™ (deferasirox) product.

The present invention provides a Exjade™ (deferasirox) formulation having a unique combination of excipients and a surfactant (e.g., a poloxamer) that are compatible with deferasiox at physiological pH environment. The invented formulation also possesses certain improved in vitro characteristics.

The invented process allows for and contributes to the high deferasirox loading. Wet granulation of the deferasirox active can be done with high drug loading (40-80% by weight) and compressed into tablets for enteric coating to achieve a final deferasirox loading of about 45-60% by weight, preferably 56% by weight.

A suitable dose of deferasirox ranges from 90 to 360 mg, especially, 90 mg, 180 mg, 360 mg unit dosage for film coated tablets and 100 to 400 mg. especially, 100 mg, 200 mg, 400 mg unit dosage for granule formulation filled into stick-packs. The dose of deferasirox administered to a patient depends on numerous factors such as weight of patient, the severity of symptom and the nature of any other drugs being administered. The current product of deferasirox is presented on the market with three dosage strengths, 125 mg, 250 mg and 500 mg. The present invention provides exemplary embodiments for manufacturing swallowable (ingestable, orally administerable) deferasirox tablets with different dissolution profiles that correspond to commercial Exjade™ (deferasirox) product From a human clinical study, the invented deferasirox formulation demonstrated higher bioavailability, as compared to the previous marketed Exjade™ (deferasirox) formulation. Therefore the therapeutic dose was adjusted accordingly to achieve comparable pharmacokinetic profile and similar therapeutic effect. In summary, the invented formulation was developed with higher deferasirox loading and superior bioavailability. Lowering the dose will eventually improve patient compliance.

In an exemplary embodiment, one or more pharmaceutically acceptable excipients are present in the deferasirox dispersible tablets, including but not limited to conventionally used excipients: at least one filler, e.g., lactose, ethylcellulose, microcrystalline cellulose; at least one disintegrant, e.g. cross-linked polyvinylpyrrolidinone. e.g. Crospovidone®; at

least one binder, e.g. polyvinylpyridone, hydroxypropylmethyl cellulose; at least one surfactant, e.g. sodium laurylsulfate, poloxamer; at least one glidant, e.g. colloidal silicon dioxide; and at least one lubricant, e.g. magnesium stearate.

In one embodiment, the deferasirox granules and film-coated tablets will include the following compendial excipients: microcrystalline cellulose, povidone, crospovidone, poloxamer 188, colloidal silicon dioxide, and magnesium stearate. Opadry coating material (hypromellose, titanium dioxide, polyethylene glycol, Macrogol, talc and FD&C blue #2/Indigo carminine aluminum lake (C.I. 7305, E132)) is used for the film-coated tablets. Among the above excipients, only poloxamer 188 and the coating material represent new excipients for Exjade; lactose and sodium lauryl sulphate would no longer be present.

Reference is made to the extensive literature on the subject for these and other pharmaceutically acceptable excipients and procedures mentioned herein, see in particular Handbook of Pharmaceutical Excipients, Third Edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete edited by H. P. Fiedler, 4th Edition. Editor Cantor, Aulendorf and earlier editions.

Suitable fillers according to the invention include but are not limited to microcrystalline cellulose, including but not limited to Avicel™ PH 102, PH 101.

Suitable disintegrants according to the invention include but are not restricted to: maize starch, CMC-Ca, CMC-Na, microcrystalline cellulose, cross-linked polyvinylpyrrolidone (PVP), e.g. as known and commercially available under the trade names Crospovidone®, Polyplasdone®, available commercially from the ISP company, or Kollidon® XL, alginic acid, sodium alginate and guar gum. In one embodiment, cross-linked PVP. e.g. Crospovidone® is used.

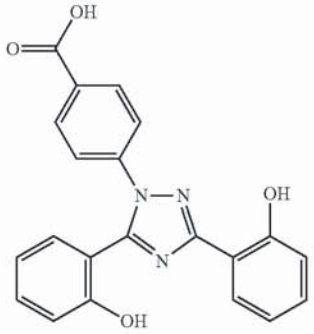
Suitableinders include but are not restricted to: starches, e.g. potato, wheat or corn starch, microcrystalline cellulose, e.g. products such as Avice®, Filtrak®, Heweten® or Pharmacel®; hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, e.g. hydroxypropylmethyl cellulose-Type 2910 USP, hypromellose, and polyvinylpyrrolidone, e.g. Povidone® K30 from BASF. In one embodiment, polyvinylpyrrolidone is used, most preferably PVP K30™.

Suitable surfactants according to the invention include but are not restricted to: sodium laurylsulfate, betain, quaternary ammonium salts, polysorbates, sorbitan erters and a poloxamer. In one embodiment, the surfactant is a poloxamer, preferably Pluronic™ F68 grade.

Suitable glidants include but are not restricted to: silica; colloidal silica, e.g. colloidal silica anhydrous, e.g. Aerosil® 200, magnesium trisilicate, powdered cellulose, starch and talc. Preferably, colloidal silicon dioxide is used.

Suitable lubricants include but are not restricted to: Mg-, Al- or Ca-stearate, PEG 4000-8000, talc, sodium benzoate, glyceryl mono fatty acid. e.g. having a molecular weight of from 200 to 800 Daltons, e.g. glyceryl monostearate (e.g. Danisco, UK), glyceryl dibehenate (e.g. Compritol ATO888™, Gattefossé France), glyceryl palmito-stearic ester (e.g. Precirol™, Gattefossé France), polyoxyethylene glycol (PEG, BASF), hydrogenated cotton seed oil (Lubitrab™, Edward Mendell Co inc), castor seed oil (Cutina™ HR, Henkel). In one embodiment, magnesium stearate is used.

Accordingly, in an exemplary embodiment, the present invention provides a tablet for treating diseases which cause an excess of metal, such as iron, in a human or animal body or are caused by an excess of metal in a human comprising Exjade™ (deferasirox) of the formula I:



I

or a pharmaceutically acceptable salt thereof present in an amount of from 45% to 60% by weight based on the total weight of the tablet where said tablet having a reduced release under gastric conditions and fast release at near neutral pH or at neutral pH.

Typically, a drug product that shows faster dissolution will have a much higher exposure level when tested in humans. Surprisingly, in the current case, Exjade™ (deferasirox) tablets formulated to have slower release showed much higher bioavailability when compared with commercial dispersible tablets, which have a faster dissolution rate but which exhibit significantly lower exposure levels. The characteristics of the new swallowable (ingestable, orally administerable) tablets, such as its disintegration time and dissolution are uniquely needed to reach the intended exposure levels.

In a separate embodiment, the present invention provides a coated tablet comprising (a) deferasirox or a pharmaceutically acceptable salt thereof, and (b) at least one pharmaceutically acceptable excipient suitable for the preparation of tablets, wherein deferasirox or a pharmaceutically acceptable salt thereof is present in an amount of from 45% to 60% by weight based on the total weight of the tablet, wherein the tablets are optionally enteric coated.

In a separate embodiment, the present invention provides a coated deferasirox tablet comprising:

(i) at least one filler in an amount of about to 10% to 40% by weight based on the total weight of the tablet;
(ii) at least one disintegrant in an amount of about 1% to 10% in weight based on the total weight of the tablet;
(iii) at least one binder in an amount of about 1% to 5% by weight based on the total weight of the tablet;
(iv) at least one surfactant in an amount of about 0.0% to 2% by weight based on the total weight of the tablet;
(v) at least one glidant in an amount of about 0.1% to 1% by weight based on the total weight of the tablet;
(vi) at least one lubricant in an amount of less than about 0.1% to 2% % by weight based on the total weight of the tablet; and
(vii) a coating, wherein the coating comprises a functional or non-functional polymer.

A. Manufacturing of Tablets by Wet Granulation Process

According to one embodiment, the present invention provides a process for the preparation of a coated deferasirox tablet according to any one of the preceding claims, which process comprises:

(i) mixing deferasirox or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient;

(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator followed by drying and screening to produce a granulate;

(iii) mixing the granulates obtained in step (ii) with at least one pharmaceutically acceptable excipient to form a mixture;

(iv) compressing the mixture obtained in step (iii) to form a tablet; and

(v) coating the tablet, wherein the coating further comprises a functional or non-functional polymer.

A flow chart showing the manufacturing process of coated deferasirox tablets prepared by wet granulation is summarized in FIG. **1**.

In accordance with the invented process, the wet granulation step is performed using 40-80% by weight of deferasirox, a poorly soluble drug with PVP K-30™ as a binding agent, Avicel™ PH 101 as a filler, crospovidone as a disintegrating agent and SLS or Poloxamer as a solubilizing agent. Water was used as granulation media. The granules were mixed with external excipients, e.g., Avicel™ PH102, crospovidone, Aerosil™ as glidant and magnesium stearate as an anti-sticking agent. The final granules were compressed into tablets and enterically coated using Acryl-EZE™ 93F, a Eudragit™ based polymer. The tablets has shown optimal hardness, friability and disintegration time. The dissolution profile of the coated deferasirox tablet is bioequivalent to the commercial Exjade (deferasirox) tablets, as shown in FIG. **2**.

Furthermore, in a related embodiment, the present invention provides a formulation with a full enteric coating. The enteric coating compris Opydrye® 03K19229 and Acryl-EZE™ was applied to a deferasirox tablet core at level of 5-15% by weight gain. An addition of sub-coating, such as Opydry™ 03K19229, enhanced the effectiveness of enteric coating. Full enteric protection is achieved after greater than 5% by weight gain. No major impact on deferasirox drug release was observed for enteric-coated deferasirox tablets after two hours acid treatment. Except for 10 minutes of the delay initially, the deferasirox drug release profiles are comparable to commercial Exjade™ (deferasirox) product, as shown in FIG. **3**.

In general, after reaching the small intestine, the enteric coated tablets release the drug slowly. However, in the present invention, the use of unique polymer, for example PVP, as binder produces fast release of drug without any significant lag time. This will be helpful for achieving bioequivalency of the formulation as compared to reference product, which is a non-enteric dispersible tablet.

The medicament of the invention may be in any suitable form including. e.g. tablets, pellets, granules, multi-particulates, beads, mini-tabs, spherules, beadlets, microcapsules, milli-spheres, nano-capsules, micro-spheres, platelets or capsules depending upon the desired route of delivery.

An embodiment provides that the medicaments such as pellet and micro-particulates are filled in capsules, caplets or the like for oral delivery.

In another embodiment, the deferasirox medicament is packaged for use by the patient or caregiver. For example, the medicament can be packaged in a foil or other suitable package and is suitable for mixing into a food product (e.g. applesauce and other food vehicles) or into a drink for consumption by a patient.

B. Manufacturing Multi-Particulates Using a Extrusion Spheronization

In a separate exemplary embodiment, the present invention provides a process for the preparation of a coated deferasirox tablet, which comprises the steps:

(i) mixing deferasirox or a pharmaceutically acceptable salt and at least one pharmaceutically acceptable excipient;

(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator;

(iii) extruding and spheronizing the wet granulates obtained in step (ii);

(iv) drying the extruded and spheronized pellets; and

(v) coating the pellets.

Accordingly, manufacturing deferasirox multi-particulates using a fluidized process technique or other pelletization techniques includes but is not limited to the following considerations:

a) Pre-wetting: Water is evenly distributed to the dry blend of drug and Avicel™ PH105 in a high shear granulator.

b) Pelletization: The pre-wetted blend was pelletized by mechanical and gravitational forces acting on the blend while being processed. Moisture (water) was constantly applied. Once the pellets reached the desired particle size range, a small percentage of the dry blend (or excipient alone) was incorporated on the pellets to stop growth and smooth the pellet surface.

c) Drying: The drying of the pellets was performed in a fluid-bed processor The pellets were dried to moisture content below 3% by weight.

The following examples illustrate aspects of the invention and are not a limitation on the present invention. Formulations for preparing tablets are set out below. In one aspect the tablets are formulated utilizing enteric coatings.

Example 1

Enteric Coated Wet Granulated Deferasirox Tablets Comprising a Surfactant, Sodium Lauryl Sulfate (SLS)

Granulation	
Internal phase	
Ingredient	**Weight % (range)**
Deferasirox	55.97%
Avicel ™ PH 101/105	14.4% (5-25)
PVP K-30 ™	2.25% (1-5)
Crospovidone	2% (1-5)
SLS	0.375% (0-1)
External phase	
Ingredient	**Weight % (range)**
Dried Granules	75%
Avicel ™ PH 102	18.5% (5-25)
Crospovidone	5% (2-10)
Aerosil ™	0.5 ranges % (0.1-1)
Magnesium Stearate	1% (0.1-2)
Subcoating	
Opadry ™ 03K19229	1% (0-2)
Enteric coating	
Eudragit ™ (Acryl EZE 93F)	7% (5-20)

Example 2

Enteric Coated Wet Granulated Deferasirox Tablets Comprising a Poloxamer (Pluronic™ F68 Grade)

Granulation	
Internal phase	
Ingredient	**Weight % (range)**
Deferasirox	55.97%
Avicel ™ PH 101/105	14.4% (5-25)
HPMc ™ 3 cps	2.25% (1-5)
Crospovidone	2% (1-5)
Pluronic ™	0.375 % (0-1)
External phase	
Ingredient	**Weight % (range)**
Dried Granules	75%
Avicel ™ PH 102	18.5% (5-25)
Crospovidone	5% (2-10)
Aerosil ™	0.5 ranges % (0.1-1)
Magnesium Stearate	1% (0.1-2)
Subcoating	
Opadry ™ 03K19229	1% (0-2)
Enteric coating	
Eudragit ™ (Acryl EZE ™ 93F)	7% (5-20)

Example 3

Composition of Deferasirox Pellets Manufactured by Extrusion-Spheronization Granulation

Ingredient	Weight % (range)
Deferasirox	60-80%
Avicel ™ PH 101/105	8-32%
PVP K-30 ™ or HPMC ™ 3 cps or HPC EXF ™	2-5%
Crosspovidone	5%
SLS/Poloxamer ™	1-2%
Enteric coating	
Eudragit ™ (Acryl EZE ™ 93F)	5-20%

Example 4

Composition of Deferasirox Pellets Manufactured by Fluidized Technique

Granulation	
Ingredient	**Weight %**
ICL670 ™	70-80%
Avicel ™ PH 105	20-30%

The compositions of the present invention and manufacturing processes provide coated tablets of Exjade (deferasirox) and thereby minimize local GI irritation. When compared to the dispersible Exjade (deferasirox) tablets having a 29.4% drug load. The present invented methods and corresponding invented improved deferasirox formulations increase the drug load for producing swallowable (ingestable) deferasirox tablets that improve patient compliance.

Example 5

Deferasirox Coated Tablets Prepared by Wet Granulation Using Non-Functional Coating

Deferasirox Tablets: Invented doses Variant A				
Component	**% (w/w) (range)**	**mg/648 mg tab**	**mg/324 mg tab**	**mg/162 mg tab**
Deferasirox	55.56	360.00	180.00	90.00
Microcrystalline cellulose PH101 ™	15.09	97.81	48.91	24.45
Microcrystalline cellulose PH102 ™	18.00	116.64	58.32	29.16
Poly Vinyl Pyrrolidone K-30 ™	2.25	14.58	7.29	3.65
Crospovidone	7.00	45.36	22.68	11.34
Pluronic ™ F68	0.10	0.65	0.32	0.16
Aerosil ™	0.50	3.24	1.62	0.81
Magnesium Stearate	1.50	9.72	4.86	2.43
Total	100.00	648.00	324.00	162.00
Coating				
Opadry ™ Blue	3.00	19.44	9.72	4.86
Final tablet weight	103.00	667.44	333.72	166.86

Invented Deferasirox Pediatric Granule Doses Variant A				
Component	**% (w/w)**	**mg/720 mg tab**	**mg/360 mg tab**	**mg/180 mg tab**
Deferasirox	55.56	400.00	200.00	100.00
Microcrystalline cellulose PH101 ™	15.09	108.68	54.34	27.17
Microcrystalline cellulose PH102 ™	18.00	129.60	64.80	32.40
Polyvinyl Pyrrolidone K-30 ™	2.25	16.20	8.10	4.05
Crospovidone	7.00	50.40	25.20	12.60
Pluronic ™ F68	0.10	0.72	0.36	0.18
Aerosil ™	0.50	3.60	1.80	0.90
Magnesium Stearate	1.50	10.80	5.40	2.70
Total	100.00	720.00	360.00	180.00

Summary of Deferasirox Variants Used in Clinical Pharmokinetic (PK) Study

Materials	Variant A Qty (%)	Variant B Qty (%)	Variant C Qty (%)
Deferasirox	55.56	55.56	54.08
Cellulose microcrystalline	15.09	14.19	13.82
Crospovidone	7.00	7.0	6.81
Polyvinylpyrrolidone K30 ™	2.25	2.25	2.19
Poloxamer ™ 188	0.10	1.00	0.97
Cellulose MKR ™ GRN	18.00	18.00	17.52

-continued

Materials	Variant A Qty (%)	Variant B Qty (%)	Variant C Qty (%)
Aerosil ™	0.50	0.50	0.49
Magnesium stearate	1.50	1.50	1.46
Eudragit ™ L 100-55	—	—	2.17
Hypromellose 5 cps	—	—	0.11
Sodium hydroxide	—	—	0.03
Triethyl citrate	—	—	0.28
Polysorbate ™ 80	—	—	0.002
Glycerol monostearate	—	—	0.06
Total weight (mg)	100.00	100.00	100.00
	Tablet properties		
Tooling	19 × 7.5 Ovaloid	19 × 7.5 Ovaloid	19 × 7.5 Ovaloid
Mean weight (mg)	910.24	916.22	903.62
Compression force (kN)	25.00	25.00	25.00
Mean hardness (N)	267.60	231.70	236.70
% friability	0.00	0.02	0.11
Dissolution Time (DT, min.) with discs	3.42	5.45	6.45

Granule Size for Deferasirox Variant A Formulation Corresponding to a Representative Batch for a Pilot Phase

		Weight of granules on screens (g) Screen Size (mm)							
		Water (%)	Water addition time (min)	LOD (%)	Bulk Density (g/ml)	Tap Density (g/ml)	1.4	1.0	0.71
Clinical Deferasirox Batch	5 Kg	26	7		0.49	0.85	0	7.4	17.1
							0.00%	7.39%	17.08%
Pilot phase DoE batch	20 Kg	26	7		0.47	0.66	0	0	3.7
							0.00%	0.00%	7.43%

		0.5	0.25	0.18	0.125	0.09	Pan	Total (g or %)
Clinical Deferasirox Batch	5 Kg	10.9	14.3	7.1	10.6	9.4	23.3	100.0
		10.89%	14.29%	7.09%	10.59%	9.39%	23.28%	100.00%
Pilot phase DoE batch	20 Kg	7.6	9.2	5.2	6.3	6.1	12.7	49.8
		15.26%	18.47%	10.44%	12.65%	10.24%	25.50%	100.00%

Patient Data from the clinical study are summarized in Table 2.

TABLE 2

PK results from deferasirox tablets prepared by wet granulation with non-functional coating

	Cmax			AUC		
	A	B	C	A	B	C
0501_00001	0.906	1.239	0.112	0.891	1.339	0.276
0501_00008	1.576	1.897	1.554	1.624	1.449	1.475
0501_00013	1.347	1.516	1.046	1.433	1.785	1.305
0501_00020	0.952	1.153	1.202	0.943	1.087	1.154

TABLE 2-continued

PK results from deferasirox tablets prepared by wet granulation with non-functional coating

	Cmax			AUC		
	A	B	C	A	B	C
0501_00023	1.727	1.225	1.765	1.567	0.974	1.574
0501_00026	0.981	1.133	1.420	0.963	0.998	1.018
0501_00027		2.293	1.122		2.477	1.015
0501_00031	1.820	2.482	1.664	2.031	3.152	2.060
0501_00035	1.778	1.517	1.672	1.246	1.015	1.249
0501_00038	1.412	1.858	1.350	1.673	2.233	1.126
0501_00049	1.714	2.233	1.467	1.929	1.525	1.752
0501_00052	1.176	1.244	1.538	1.774	1.564	1.538
0501_00053	1.057	1.340	1.091	0.894	1.269	1.138
0501_00054	0.781	0.769	0.369	0.791	0.789	0.380
0501_00055	1.652	1.326	1.380	2.039	1.094	2.672
0501_00075	1.317	1.268	1.380	1.010	1.388	1.318
0501_00088	1.604	1.580	0.921	1.552	1.452	1.075
0501_00093	1.689	1.713	1.976	1.767	1.924	1.472
0501_00104	1.827	1.556	1.519	1.489	1.360	1.495
0501_00107	1.352	1.060	0.725	1.370	1.357	0.614

The dissolution profile for clinical deferasirox variants A, B, and C (500 MG) is highlighted in Table 3.

TABLE 3

Dissolution data for Clinical Variants A, B, and C (500 mg).

Treatment	Geo-mean ratio	90% CI Lower	90% CI Upper
A: 500 mg tablet with 0.1% Pluronic ™	1.38	1.18	1.62
B: 500 mg tablet with 1.0% Pluronic ™	1.43	1.22	1.67

TABLE 3-continued

Dissolution data for Clinical Variants A, B, and C (500 mg).

Treatment	Geo-mean ratio	90% CI Lower	90% CI Upper
C: 500 mg tablet with 1.0% Pluronic ™ + modified-release enteric coating	1.15	0.99	1.35

Data for C_{max} were comparable to those for AUC.
Median T_{max} (3-4 hrs) appeared to be similar with all formulations.
Deferasirox PK was slightly less variable with variants A, and B (CV 23-38%), and slightly more variable with variant C (CV 54-61%) as compared to a conventional marketed commercial formulation (CV 31-49%).
PK data with the current formulation in this study were consistent with data from previous studies.

Example 6

High Load Deferasirox Formulation No Food Effect Studies

Six clinical studies have been initiated with corresponding pharmacology studies in healthy adult volunteers. Four studies have been completed and two studies are ongoing. In the initial clinical pharmacology study for variant selection (study 1), the tablet variant selected for development displayed suprabioavailability: both AUC and C_{max} for the invented deferasirox formulation were approximately 40% higher compared to the current dispersible tablet (DT) at a single dose of 1500 mg. Therefore, the subsequent clinical pharmacology studies used strength-adjusted formulations (400 mg granules and 360 mg FCT to match the 500 mg DT), in line with EMA/618604/2008 Rev. 7, which states that "If suprabioavailability is found, development of a lower dosage strength should be considered".

Study 2 (pivotal study with FCT) and study 3 (pilot study with granules) both demonstrated fully equivalent exposure with an AUC_{last} ratio of 100%. However. C_{max} did not meet the standard bioequivalence criteria (as summarized in Table 4): values were higher for both strength-adjusted formulations.

The food effect study 4 (granules) showed overall equivalence of the administration with a soft food (apple sauce or yogurt) or with a low-fat meal when compared to fasting intake with water. The exposure after administration with a high-fat meal was close to the equivalence limits of 80% to 125% for AUC_{last}.

TABLE 4

Summary of pharmacokinetic comparisons for invented deferasirox formulation

Study No.	N	deferasirox dose [mg] (form)	food	AUClast ratio (90% CI)	Cmax ratio (90% CI)
Completed Studies					
1	2	1500 (F)/	fasted/fasted	**1.38**	**1.39**
	0	1500 (DT)		(1.179-**1.620**)	(1.164-**1.661**)
2	3	1080 (F)/	fasted/fasted	1.00	**1.30**
	2	1500 (DT)		(0.932-1.078)	(1.203-**1.400**)
3	2	1200 (G)/	fasted/fasted	1.00	1.18
	0	1500 (DT)		(0.915-1.099)	(1.050-**1.323**)
4	2	1200 (G)/	applesauce/	0.996	0.972
	4	1200 (G)	water	(0.934-1.063)	(0.891-1.061)
		1200 (G)/	yogurt/water	0.986	0.988
		1200 (G)		(0.924-1.052)	(0.905-1.077)
	2	1200 (G)/	breakfast/	0.917	0.887
	4	1200 (G)	water	(0.845-0.995)	(**0.789**-0.997)

TABLE 4-continued

Summary of pharmacokinetic comparisons for invented deferasirox formulation

Study No.	N	deferasirox dose [mg] (form)	food	AUClast ratio (90% CI)	Cmax ratio (90% CI)
		1200 (G)/ 1200 (G)	high-fat breakfast/ water	1.194 (1.099-**1.298**)	0.949 (0.843-1.069)
Ongoing Studies (results expected by Dec 2013)					
5		1080 (F)/ 1080 (F)	fed/fasted	TBD	TBD
6		1200 (G)/ 1500 (DT)	fasted/fasted	TBD	TBD

DT: dispersible tablets (current formulation);
F: film-coated tablets;
G: granules;
N = number of subjects.
Study 3 also tested dose linearity (at 400 mg/800 mg/1200 mg) for the granules.
Values outside the equivalence limits [0.8-1.25] are highlighted in **bold**

The two remaining clinical pharmacology studies (to be conducted in 2H2013) aim to confirm the comparative bioavailability results for the granules, and to test the food effect for the FCT.

The new Exjade formulations represent a significant improvement in patient care and support compliance with chelation therapy because of the improved pharmaceutical properties and because of the changes in composition. These improvements are expected to provide for a positive benefit risk due to the importance of compliance/adherence to chelation therapy for patients with chronic iron overload aged 2 years and older:

- a lower inter-subject variability in exposure (CV % geometric mean in study F2102 for FCT and DT: AUC_{last} 39.2% vs 49.7%, Cmax 27.5% vs 33.4%, respectively) and the absence of a substantial food effect (study 4) suggest that the new formulations achieve a more predictable dose-exposure relationship in clinical practice.
- the absence of a substantial food effect (study 4) which obviates the requirement to take the drug on an empty stomach at least 30 minutes before food and therefore allows patients more convenience and flexibility in the scheduling and administration of their daily dose.
- a more palatable alternative to the currently approved dispersion, particularly for elderly and pediatric patients (an aspect that was investigated in one of the measures of the currently approved Exjade EU PIP).

The currently approved Exjade tablet is formulated with sodium lauryl sulphate, which may be associated with gastrointestinal tract irritation. Exjade currently also contains lactose and so is not recommended in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or severe lactase deficiency. Novartis believes the exclusion of lactose and sodium lauryl sulfate in the new formulations will improve the gastrointestinal tolerability of the product. This is supported by the recently completed one year study 2209 where NTDT patients in the placebo arm, which contained the same excipients as the currently marketed Exjade formulation, reported GI adverse event rates that were comparable to the active treatment arm (42.9% for placebo vs. 36.4% for Exjade 10 mg/kg).

While the 90% CI for Cmax with both the FCT (in the pivotal study 2) and the granules (in the pilot study) were not fully contained within the equivalence limits of 80% to 125%, the observed differences in C_{max} not clinically meaningful for the new formulations of this innovator drug based on the following rationale:

total drug exposure (AUC) is the key parameter predicting safety and efficacy of deferasirox; chelation efficacy for iron chelators is commonly accepted to be related to AUC. In a 24-hour PK study following a single 35 mg/kg dose of oral deferasirox that was published by Chirnomas et al (2009), patients with inadequate response to deferasirox had significantly lower systemic drug exposure compared with control patients (P<0.00001). C_{max}, volume of distribution/bioavailability (Vd/F), and elimination half-life (t(½)) were not different between the groups.

no effect on the QT interval (a typical C_{max}-related toxicity) was observed in the thorough QT study (submitted with the original application in 2005): in that study, healthy volunteers (in whom exposure is higher than in iron-overloaded patients) were given doses of up to 40 mg/kg in order to achieve high Cmax levels

the range of Cmax values observed in previous healthy volunteer studies with over 200 subjects is consistent with the range of C_{max} values observed with the new formulations (see below)

a large amount of safety, efficacy and exposure data exist for the current formulation (see below for details)

in previously submitted patient studies, only minor safety findings such as nausea and headaches were noted at T_{max} (see below for details)

a statistical analysis to correlate pharmacokinetic parameters (Ctrough as a proxy of AUC, C2h as a proxy for Cmax) with renal effects in the large, one year patient study A2409 indicates that creatinine changes are more strongly correlated with AUC than with Cmax (see below for details)

Exjade™ (deferasirox) is titrated based on efficacy and tolerability: the recommended starting dose is 20 mg/kg/day, with up-titration recommended in 5-10 mg/kg steps every 3-6 months. Therefore, patients would only be exposed to the highest approved dose (40 mg/kg/day for the current formulation) after an extended period of up-titration with confirmed tolerability

the absence of a significant food effect results in a lower risk of increased exposure when the drug is taken with a meal. With the currently approved DT formulation, ingestion of 20 mg/kg with a high fat meal (previous study for commercially marketed formulation) resulted in an average Cmax of 138 μM in healthy volunteers, whereas dispersion in water (study 2120) resulted in a lower Cmax of 71 μM in healthy volunteers. In the patient study A0105F, exposure nearly doubled (to a variable extent) when Exjade was given after a high-fat breakfast. No such effect was observed with the new granule formulation (Table 4).

FIG. **7** summarizes mean concentration (μmol/L)-time profiles of the key pharmacokinetic results for studies 1 (non-strength-adjusted tablet comparison), 2 (pivotal strength-adjusted FCT study), 3 (pilot strength-adjusted granule study), and 4 (granule food-effect study).

Individual C_{max} values from Study 2 and Study 3 are within the range of historical C_{max} values observed with the current commercially marketed DT formulation: FIG. **8** includes C_{max} data from (1) previous CP studies in healthy subjects given 20 mg/kg deferasirox DT, (2) FCT treatment in Study 2, and (3) granule treatment in Study 3.

Clinical data has been generated and analyzed from a one-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral deferasirox formulation (20 mg/kg/day) in 1744 patients with transfusion dependent iron overload; thalassemia, MDS, SCD, and rare anemias (Study 7). Study 7 used sparse PK sampling: in addition to efficacy and safety data, deferasirox PK data were collected in a large sub-group of patients (~600) at pre-dose (C_{trough}, a proxy for AUC) and 2 hours post-dose (C2h; a proxy for Cmax) on day 1, week 12 and week 28. As shown in FIG. **9**, the C_{max} values for the new high load deferasirox formulations at steady-state (predicted by a nonparametric superposition approach) in studies 2 and 3 lie within the range of observed steady-state deferasirox C2h values with the current DT formulation. Of note, deferasirox exposure in healthy subjects is generally higher than in iron-overloaded patients; in addition, the sampling time point in Study 7 (C2h) underestimates C_{max} (since deferasirox T_{max} usually occurs between 2 and 4 hours post-dose). Since clinical safety data were assessed within this range of C_{max}, it is unlikely that C_{max} observed with the new formulations would lead to additional safety issues.

Deferasirox Cmax values in healthy volunteers are generally higher than in patients. Two healthy volunteer studies in the initial registration package in 2005 were therefore reviewed for potential Cmax-related adverse events. In the thorough QT healthy volunteer study (which found no effect of Exjade on the QT interval), 44 volunteers received Exjade™ (deferasirox 40 mg/kg immediately after consumption of a high-fat breakfast to maximize C_{max}. C_{max} averaged 256 μM (range 134-472 μM). Safety findings in these subjects were limited to GI symptoms (diarrhea/loose stools, flatulence, and nausea) in 18% of patients, and headache and dizziness in one patient each (2%). In a study (a randomized crossover study in 28 healthy volunteers to evaluate the bioequivalence of a single 20 mg/kg dose of Exjade™ dispersed in fruit juice or water), three HV subjects reported loose stools 2.5 to 5 hours after Exjade intake, each on two separate occasions, lasting for 5-30 minutes.

In addition, a new analysis of creatinine and creatinine clearance changes was performed to explore whether deferasirox-associated renal changes are a function of peak exposure (C_{max}) or of overall exposure (AUC). The analysis used data from the large multicenter study 7, in which C_{trough} (a proxy of AUC) and deferasirox C2h (a proxy of C_{max}) was collected at multiple time points. Even though both PK parameters correlate with dose, the analyses summarized below indicate that renal functional changes are more closely associated with AUC than with C_{max}.

Based on study 7 data, the relationship between PK parameters at steady state (C_{trough} and C2h) and serum creatinine was investigated by using a linear mixed model of log-transformed creatinine values (1990 observations at week 12 and 28) with patient included in model as a random effect. After log-transformation, baseline creatinine levels, C2h and C_{trough} were included as predictors in the model. As shown in Table 5, a far higher slope (estimate) was observed for log (C_{trough}) than for log(C2h), indicating a higher correlation with Ctrough (a proxy of AUC) than with C2h (a proxy of C_{max}). For a 30% increase in C_{max} (as observed for the FCT), the serum creatinine ratio would be 1.0087 (=1.3^0.03287) with upper bound of the 95% CI of 1.0127 (with all other factors held constant). The potential of multicolinearity for log(C2h) and log(C_{trough}) was assessed in the statistical model described above and did not show any multicolinearity issue (Variance Inflation Factor (VIF)=1.56 and condition index<30).

TABLE 5

Linear mixed effect model of percent change in serum creatinine for deferasirox formulations

Parameter	Estimate	Standard error	T value	Pr > |t|	Lower	Upper
Log (baseline creatinine)	0.9593	0.01226	78.22	<0.0001	0.9391	0.9795
Log (C2h)	0.03287	0.007786	4.22	<0.0001	0.02005	0.04569
Log (C_{trough})	0.06504	0.004803	13.54	<0.0001	0.05713	0.07295

Day 1 C2h values did not predict the extent of creatinine changes at week 4 (N=682): the slope of the linear regression between Day 1 C2h and percent change in serum creatinine at week 4 was 0.03 (−0.01, 0.08), with a p-value of 0.22, and R-square<0.01, as summarized in FIG. **11**.

There was no statistical difference in the rate of serum creatinine increases (either >33% over baseline, or >33% over baseline and >ULN) between patients whose C2h value was below the median (56.5 μmol/L in this analysis) and those whose C2h value was at or above the median, based on the Chi-square test in a population exposed to a dose of approximately 20 mg/kg (N=528; Table 6). A similar analysis was performed considering another classification for Day 1 C2h using quartiles (<Q1; Q1-<median; median-<Q3; ≥Q3) and results led to the same conclusion.

TABLE 6

Statistical analysis of C2h on day 1 versus notable serum creatinine values at week 4 (dose range 17.5-22.5 mg/kg) for deferasirox formulation

	Day 1 C2h < median (N = 264); % (N)	Day 1 C2h ≥ median (N = 264); % (N)	Chi-square test p-value
SCr increase >33% from baseline at week 4	14.39% (38)	18.56% (49)	0.197 (NS)
SCr increase >33% from baseline and >ULN at week 4	5.68% (15)	7.58% (20)	0.382 (NS)

A covariate analysis by an ordinal logistic regression model was performed to further elucidate the impact of each PK parameter on renal function, as summarized in Table 7. C_{trough} had a strong impact on creatinine clearance (CRCL) change in categories, but C2h had almost no impact (p-value=0.994), after adjusting for Ctrough. A C2h increase by 1.3-fold would provide an odds ratio (OR) of 0.999 (0.872; 1.146). This suggests that the new invented deferasirox formulations (comparable AUC but higher C_{max} than the current marketed formulation) would result in a comparable effect on renal function.

All analyses summarized in this section will be described in full detail in the registration dossiers for the FCT and the granules.

TABLE 7

Summary results of ordinal logistic regression model analysis based on week 12 data

Parameter	Estimate	Std error	Pr > ChiSq	OR* for a 2-fold increase in PK parameter (95% CI)	OR* for a 30% increase in PK parameter (95% CI)
Log(baseline creatinine clearance)	−10.3474	0.6405	<0.0001		
Log(C2h)	−0.00203	0.2663	0.9939	0.999 (0.695, 1.434)	0.999 (0.872; 1.146)
Log(C_{trough})	0.9346	0.1653	<0.0001	1.911 (1.527, 2.393)	1.278 (1.174; 1.391)

Response profile based on the following CrCl Categories (with ordered value):
1: 90 ml/min or more (N = 766);
2: 60 to <90 ml/min (N = 193);
3: 15 to <60 ml/min (N = 77);
*OR: Odds Ratio

REFERENCES

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Osborne R H, Lourenco R D, Dalton A. et al (2007). Quality of life related to oral versus subcutaneous iron chelation: A time trade-off study. Value Health 10:451-456.

It is understood that while the present invention has been described in conjunction with the detailed description thereof that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the following claims. Other aspects, advantages and modifications are within the scope of the claims.

What is claimed:

1. A tablet for oral administration consisting of 90 mg deferasirox;
53.61 mg microcrystalline cellulose;
3.65 mg poly vinyl pyrrolidone K-30;
11.34 mg crospovidone;
0.16 mg poloxamer;
0.81 mg fumed silica;
2.43 mg magnesium stearate; and
4.86 mg seal-coat.

2. A tablet for oral administration consisting of 180 mg deferasirox;
107.23 mg microcrystalline cellulose;
7.29 mg poly vinyl pyrrolidone K-30;
22.68 mg crospovidone;
0.32 mg poloxamer;
1.62 mg fumed silica;
4.86 mg magnesium stearate; and
9.72 mg seal-coat.

3. A tablet for oral administration consisting of 360 mg deferasirox;
215.45 mg microcrystalline cellulose;
14.58 mg poly vinyl pyrrolidone K-30;

45.36 mg crospovidone;
0.65 mg poloxamer;
3.24 mg fumed silica;
9.72 mg magnesium stearate; and
19.44 mg seal-coat.

* * * * *

Exhibit B

Paragraph IV Patent Certifications
November 19, 2019

DRUG NAME	DOSAGE FORM	STRENGTH	RLD/NDA	DATE OF SUBMISSION	NUMBER OF ANDAs SUBMITTED	180-DAY STATUS	180-DAY DECISION POSTING DATE	DATE OF FIRST APPLICANT APPROVAL	DATE OF FIRST COMMERCIAL MARKETING BY FTF	EXPIRATION DATE OF LAST QUALIFYING PATENT
Abacavir Sulfate	Tablets	300 mg	Ziagen 20977	1/28/2009						
Abacavir	Oral Solution	20 mg/mL	Ziagen 20978	12/27/2012						
Abacavir Sulfate, Dolutegravir and Lamivudine	Tablets	600 mg/50 mg/300 mg	Triumeq 205551	8/14/2017						
Abacavir Sulfate and Lamivudine	Tablets	600 mg/300 mg	Epzicom 21652	9/27/2007						
Abacavir Sulfate, Lamivudine and Zidovudine	Tablets	300 mg/150 mg/300 mg	Trizivir 21205	3/22/2011						
Abiraterone Acetate	Tablets	125 mg	Yonsa 210308	7/23/2018	1					3/17/2034
Abiraterone Acetate	Tablets	250 mg	Zytiga 202379	4/28/2015	13	Eligible	6/18/2019	10/31/2018	11/21/2018	8/24/2027
Abiraterone Acetate	Tablets	500 mg	Zytiga 202379	8/23/2017	1					8/24/2027
Acarbose	Tablets	25 mg, 50 mg and 100 mg	Precose 20482	3/22/2005						
Acetylcysteine	Injection	200 mg/mL, 30 mL vials	Acetadote 21539	4/4/2012						
Acetaminophen*	Injection	1000 mg/100 mL (10 mg/mL)	Ofirmev 22450	4/7/2011						
Acetaminophen	Extended-release Tablets	650 mg	Tylenol 19872							
Acetaminophen and Tramadol Hydrochloride	Tablets	325 mg/ 37.5 mg	Ultracet 21123							
Acetaminophen/ Aspirin/ Caffeine	Tablets	250 mg/ 250 mg/ 65 mg	Excedrin (migraine) 20802							
Acyclovir Sodium	Injection	50 mg/mL, 10 mL and 20 mL vials	Zovirax 18603							
Adapalene	Topical Gel	0.30%	Differin 21753	9/15/2009						
Adapalene and Benzoyl Peroxide	Gel	0.1%/2.5%	Epiduo 22320	12/30/2011						
Adapalene and Benzoyl Peroxide	Gel	0.3%/2.5%	Epiduo Forte 207917	5/4/2016	1	Eligible	6/18/2019	10/17/2018		3/12/2023
Adefovir Dipivoxil	Tablets	10 mg	Hepsera 21449	6/8/2010						
Afatinib Dimaleate	Tablets	20 mg, 30 mg and 40 mg	Gilotrif 201292	7/12/2017						
Adenosine	Injection	3 mg/mL, 20 mL and 30 mL vials	Adenoscan 20059	4/16/2005						

Paragraph IV Patent Certifications
November 19, 2019

DRUG NAME	DOSAGE FORM	STRENGTH	RLD/NDA	DATE OF SUBMISSION	NUMBER OF ANDAs SUBMITTED	180-DAY STATUS	180-DAY DECISION POSTING DATE	DATE OF FIRST APPLICANT APPROVAL	DATE OF FIRST COMMERCIAL MARKETING BY FTF	EXPIRATION DATE OF LAST QUALIFYING PATENT
Dapaglifozin and Metformin Hydrochloride	Extended-release Tablets	5 mg/500 mg 5 mg/1000 mg 10 mg/500 mg 10 mg/1000 mg	Xigduo XR 205649	1/8/2018						
Dapsone	Gel	7.5%	Aczone 207154	2/13/2017	1	Eligible	7/2/2019	6/26/2019		11/18/2033
Daptomycin	For Injection	500 mg/vial	Cubicin 21572	11/19/2008	1	Extinguished	11/19/2019			
Darifenacin Hydrobromide	Extended-release Tablets	7.5 mg and 15 mg	Enablex 21513	12/22/2008						
Darunavir Ethanolate	Tablets	75 mg, 150 mg and 300 mg	Prezista 21976	6/23/2010	1					12/26/2026
Darunavir Ethanolate	Tablets	400 mg	Prezista 21976	6/23/2010	2					12/26/2026
Darunavir Ethanolate	Tablets	600 mg	Prezista 21976	6/23/2010	3	Deferred	7/2/2019	11/21/2017		12/26/2026
Darunavir Ethanolate	Tablets	800 mg	Prezista 21976	5/14/2013	1					12/26/2026
Dasatinib	Tablets	80 mg and 140 mg	Sprycel 21986	6/17/2011						
Dasatinib	Tablets	20 mg, 50 mg, 70 mg and 100 mg	Sprycel 21986	6/28/2010						
Deferasirox	Tablets for Suspension	125 mg, 250 mg, and 500 mg	Exjade 21882	10/28/2011	1	Eligible	7/2/2019	1/26/2016	3/22/2019	4/5/2019
Deferasirox *	Tablets	90 mg and 360 mg	Jadenu 206910	10/19/2015	1	Extinguished	7/16/2019			4/5/2019
Deferasirox	Tablets	180 mg	Jadenu 206910	4/21/2016	1	Eligible	7/16/2019			11/21/2034
Deferiprone	Tablets	500 mg	Ferriprox 21825	1/29/2016	1	Eligible	8/13/2019	2/8/2019		6/28/2021
Deoxycholic Acid	Injection	10 mg/mL (2 mL)	Kybella 206333	7/13/2018						
Desflurane	Inhalation	99.9%	Suprane 20118	9/11/2008						
Desloratadine	Tablets	5 mg	Clarinex 21165	6/21/2006						
Desloratadine	Orally Disintegrating Tablets	2.5 mg and 5 mg	Clarinex 21165	6/21/2006						
Desloratadine	Oral Solution	0.5 mg/mL	Clarinex Syrup 21300	5/8/2008						

Exhibit C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS CORPORATION, NOVARTIS AG, and NOVARTIS PHARMA AG Plaintiffs, v. ACTAVIS, INC. and ACTAVIS ELIZABETH LLC Defendants.	C.A. No. 15-1219-RGA

STIPULATION AND ORDER OF DISMISSAL WITHOUT PREJUDICE

1. This action arises out of the filing of Abbreviated New Drug Application ("ANDA") No. 208697 with the United States Food and Drug Administration by Actavis, Inc. and Actavis Elizabeth LLC (collectively, "Defendants"), with a certification under 35 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certification"), seeking approval to manufacture, market, and sell 90 mg, 180 mg, and 360 mg generic deferasirox tablets (collectively, the "Actavis Generic Deferasirox Tablets") before the expiration of U.S. Patent No. 6,465,504 (the "'504 Patent") on the basis that certain claims of the '504 Patent are allegedly invalid or will allegedly not be infringed by the manufacture, use, or sale of the Actavis Generic Deferasirox Tablets.

2. On September 15, 2017, Defendants withdrew the Paragraph IV Certification with respect to the '504 Patent in ANDA No. 208697 and replaced it with a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(III) attesting that Defendants are not seeking approval to manufacture, market, or sell any Actavis Generic Deferasirox Tablets prior to the expiration of the '504 Patent.

3. Defendants hereby affirm that neither of them will further amend ANDA No. 208697 to include a Paragraph IV Certification with respect to the '504 Patent unless and until

the '504 Patent is held invalid or unenforceable by a court decision from which no appeal has been or can be taken.

NOW, THEREFORE, IT IS HEREBY STIPULATED AND AGREED, by and between the parties and subject to the approval of the Court, that pursuant to Federal Rules of Civil Procedure 41(a) and 41(c), the claims and counterclaims in this action are hereby dismissed without prejudice with each party to bear its own costs, expenses, and attorneys' fees. For the avoidance of doubt, this stipulation has no effect on the action captioned *Actavis Elizabeth LLC v. Novartis Pharmaceuticals Corp. et al.*, C.A. No. 16-604-RGA, pending in this Court.

/s/ Daniel M. Silver
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Daniel M. Silver (#4758)
Benjamin A. Smyth (#5528)
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Attorneys for Defendants

Dated: September 15, 2017

SO ORDERED this 18 day of Sept, 2017.

THE HONORABLE RICHARD G. ANDREWS
UNITED STATES DISTRICT JUDGE

Exhibit D

[redacted]

Alembic
Touching Lives over 100 years

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Alembic
Touching Lives over 100 years

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Alembic
Touching Lives over 100 years

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Touching Lives over 100 years

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Alembic
Touching Lives over 100 years

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Exhibit E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re/application of: **Indrajit Ghosh , and Jia-Ai Zhang**	Examiner: **MILLIGAN, ADAM C** Art Unit: **1612**
Application No.: **14/198,872**	Confirmation No.: **3053**
Filing Date: **March 6, 2014**	Atty. Docket No. **PA055541-US-NP**
Title: **ORAL FORMULATIONS OF DEFERASIROX**	Customer No. **3705**

PRELIMINARY AMENDMENT TO EXPEDITE PROSECUTION

December 15, 2015

Mail Stop: Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

Prior to examination on the merits Applicants respectfully request the application be amended as follows, without prejudice, to expedite prosecution. Applicants respectfully submit this case is now "ready for final conclusion" under MPEP §708. APPLICANTS RESPECTFULLY REQUEST A FIRST ACTION INTERVIEW IN THE ABOVE-IDENTIFIED APPLICATION.

CLAIMS begin on Page 2.

REMARKS begin on Page 11.

CLAIMS

Claim 1. (Withdrawn): An orally administerable medicament comprising: deferasirox or a pharmaceutically acceptable salt thereof present in an amount of from 45% to 60% by weight based on the total weight of the medicament, said medicament having reduced release under gastric conditions and fast release at near neutral pH or at neutral pH.

Claim 2. (Withdrawn): An orally medicament comprising (a) deferasirox or a pharmaceutically acceptable salt thereof; and (b) at least one pharmaceutically acceptable excipient suitable for the preparation of medicament, wherein deferasirox or a pharmaceutically acceptable salt thereof is present in an amount of from 45% to 60% by weight based on the total weight of the medicament.

Claim 3. (Withdrawn): The orally administerable medicament according to claim 1 in tablet form.

Claim 4. (Withdrawn): The orally administerable medicament according to claim 1 in pellet form or multi-particulate form.

Claim 5. (Withdrawn): The orally administerable medicament according to claim 1 in tablet form that possesses a disintegration time of 5-10 minutes when measured by a standard USP disintegration test.

Claim 6. (Withdrawn): The orally administerable medicament according to claim 5 further comprising an enteric coating.

Claim 7. (Withdrawn): The orally administerable medicament according to claim 1

further comprising:

(i) at least one filler in a total amount of about to 10% to 40 % by weight based on the total weight of the tablet;

(ii) at least one disintegrant in a total amount of about 1% to 10% by weight based on the total weight of the tablet;

(iii) at least one binder in a total amount of about 1% to 5% by weight based on the total weight of the tablet;

(iv) at least one surfactant in a total amount of about 0.0% to 2% by weight based on the total weight of the tablet;

(v) at least one glidant in a total amount of about 0.1% to 1% by weight based on the total weight of the tablet;

(vi) at least one lubricant in a total amount of less than about 0.1% to 2% by weight based on the total weight of the tablet; and

(vii) a coating, wherein the coating further comprises a functional or a non-functional polymer.

Claim 8. (Withdrawn): The medicament according to claim 7 wherein the surfactant is selected from sodium laurel sulfate and a poloxamer.

Claim 9. (Withdrawn): The medicament according to claim 8 wherein said surfactant is the polaxamer Pluronic™ F68 grade.

Claim 10. (Withdrawn): The medicament according to claim 7 wherein said medicament is further seal-coated, wherein said seal-coat is Opadry™ 03K19229 1% (0-2%).

Claim 11. (Withdrawn): The medicament according to claim 7 wherein said

medicament comprises an enteric coating, where said enteric coating is selected from Eudragit™ (Acryl EZE™ 93F) at 7% (5-20%).

Claim 12. (Withdrawn): The medicament according to anyone of claims 1 containing deferasirox in its free acid form in an amount of about 50 mg to 600 mg .

Claim 13. (Withdrawn): A process for manufacturing deferasirox medicament according to claim 3 in the form of tablets, granules, pellets or multi-particulates comprising the steps of:

(i) mixing deferasirox and at least one pharmaceutically acceptable excipient;

(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator followed by drying and screening to produce granulates;

(iii) mixing the granulates obtained in step (ii) with at least one pharmaceutically acceptable excipient to form a mixture;

(iv) compressing the mixture obtained in step (iii) to form a tablet; and

(v) coating the tablet.

Claim 14. (Withdrawn): A process for the preparation of a coated deferasirox tablet, comprising the steps of:

(i) mixing deferasirox or a pharmaceutically acceptable salt and at least one pharmaceutically acceptable excipient;

(ii) wet-granulating the mixture obtained in step (i) in a high shear granulator;

(iii) extruding and spheronizing the wet granulates obtained in step (ii);

(iv) drying the extruded and spheronized pellets; and

(v) coating the pellets.

Claim 15. (Withdrawn): A method of treating diseases which cause an excess of metal

in a human or animal body or are causes by an excess of metal in a human or animal body comprising the step of administering a medicament according to claim 1 comprising about 50 mg to about 600 mg of a deferasirox or pharmaceutically acceptable salt thereof.

Claim 16. (Withdrawn): The method according to claim 15 wherein the metal is iron.

Claim 17. (Withdrawn): An orally administerable tablet in specific dosage forms comprising:

Component	% (w/w)	mg/648mg tab	mg/324mg tab	mg/162mg tab
Deferasirox	**55.56**	360.00	180.00	90.00
Microcrystalline cellulose PH101	**15.09**	97.81	48.91	24.45
Microcrystalline cellulose PH102	**18.00**	116.64	58.32	29.16
Poly Vinyl Pyrrolidone K-30	**2.25**	14.58	7.29	3.65
Crospovidone	**7.00**	45.36	22.68	11.34
Pluronic F68	**0.10**	0.65	0.32	0.16
Aerosil	**0.50**	3.24	1.62	0.81
Magnesium Stearate	**1.50**	9.72	4.86	2.43
Total	**100.00**	**648.00**	**324.00**	**162.00**
Coating				
Opadry Blue	**3.00**	19.44	9.72	4.86
Final tablet weight	**103.00**	**667.44**	**333.72**	**166.86**

Claim 18. (Withdrawn): An orallyadministrable pellet, as specific pediatric dosage forms, comprising:

Component	% (w/w)	mg/720mg	mg/360mg	mg/180mg

		tab	tab	tab
Deferasirox	**55.56**	400.00	200.00	100.00
Microcrystalline cellulose PH101™	**15.09**	108.68	54.34	27.17
Microcrystalline cellulose PH102™	**18.00**	129.60	64.80	32.40
Poly Vinyl Pyrrolidone K-30™	**2.25**	16.20	8.10	4.05
Crospovidone	**7.00**	50.40	25.20	12.60
Pluronic™ F68	**0.10**	0.72	0.36	0.18
Aerosil™	**0.50**	3.60	1.80	0.90
Magnesium Stearate	**1.50**	10.80	5.40	2.70
Total	**100.00**	**720.00**	**360.00**	**180.00**

Claim 19. (Withdrawn): An orally administerable medicament comprising a plurality of deferasirox pellets or multi-particulates, wherein each said pellets or multi-particulates comprises deferasirox, or a pharmaceutically acceptable salt thereof, present in an amount of from 45% to 60% by weight based on the total weight of the medicament, said medicament having reduced release under gastric conditions and a fast release at near neutral pH or at neutral pH.

Claim 20. (Withdrawn): The orally administerable medicament according to claim 19, comprising about 50 mg to about 600 mg of deferasirox, based upon the weight of free deferasirox.

Claim 21. (Withdrawn): The orally administerable medicament according to claim 20, wherein said plurality of pellets or multi-particulates are included in a capsule.

Claim 22. (Withdrawn): The orally administerable medicament according to claim 1, wherein the amount of deferasirox loading is increased using wet granulation or extrusion spheronization, as compared to a disperable deferasirox tablet formulation.

Claim 23. (Withdrawn): The orally administerable medicament according to claims 1, wherein the bioavailability of deferasirox is increased using wet granulation or extrusion spheronization, as compared to a disperable deferasirox tablet formulation.

Claim 24. (Withdrawn): The orally administerable medicament according to claim 23, wherein a decreased deferasirox dosage achieves a similar therapeutic efficacy as compared to a higher dosage disperable deferasirox tablet formulation.

Claim 25. (New): A tablet for oral administration comprising 90mg deferasirox; and,

(i) at least one filler in a total amount of about to 10% to 40 % by weight based on the total weight of the tablet;

(ii) at least one disintegrant in a total amount of about 1% to 10% by weight based on the total weight of the tablet;

(iii) at least one binder in a total amount of about 1% to 5% by weight based on the total weight of the tablet;

(iv) at least one surfactant in a total amount of about 0.0% to 2% by weight based on the total weight of the tablet;

(v) at least one glidant in a total amount of about 0.1% to 1% by weight based on the total weight of the tablet;

(vi) at least one lubricant in a total amount of less than about 0.1% to 2% by weight based on the total weight of the tablet; and

(vii) a coating, wherein the coating further comprises a polymer; and,

wherein the tablet possesses a disintegration time of 5-10 minutes when measured by a standard USP disintegration test.

Claim 26. (New): A tablet for oral administration according to claim 25 comprising,

24.45mg microcrystalline cellulose PH101;

29.16mg microcrystalline cellulose PH102;

3.65mg poly vinyl pyrrolidone K-30;

11.34mg crospovidone;

0.16mg pluronic F68;

0.81mg aerosil;

2.43mg magnesium stearate; and,

4.86mg opadry blue coating.

Claim 27. (New): A tablet for oral administration comprising 180mg deferasirox; and,

(i) at least one filler in a total amount of about to 10% to 40 % by weight based on the total weight of the tablet;

(ii) at least one disintegrant in a total amount of about 1% to 10% by weight based on the total weight of the tablet;

(iii) at least one binder in a total amount of about 1% to 5% by weight based on the total weight of the tablet;

(iv) at least one surfactant in a total amount of about 0.0% to 2% by weight based on the total weight of the tablet;

(v) at least one glidant in a total amount of about 0.1% to 1% by weight based on the total weight of the tablet;

(vi) at least one lubricant in a total amount of less than about 0.1% to 2% by weight based on the total weight of the tablet; and

(vii) a coating, wherein the coating further comprises a polymer; and,

wherein the tablet possesses a disintegration time of 5-10 minutes when measured by a standard USP disintegration test.

Claim 28. (New): A tablet for oral administration according to claim 27 comprising,

48.91mg microcrystalline cellulose PH101;

58.32mg microcrystalline cellulose PH102;

7.29mg poly vinyl pyrrolidone K-30;

22.68mg crospovidone;

0.32mg pluronic F68;

1.62mg aerosil;

4.86mg magnesium stearate; and,

9.72mg opadry blue coating.

Claim 29. (New): A tablet for oral administration comprising 360mg deferasirox;

and,

(i) at least one filler in a total amount of about to 10% to 40 % by weight based on the total weight of the tablet;

(ii) at least one disintegrant in a total amount of about 1% to 10% by weight based on the total weight of the tablet;

(iii) at least one binder in a total amount of about 1% to 5% by weight based on the total weight of the tablet;

(iv) at least one surfactant in a total amount of about 0.0% to 2% by weight based on the total weight of the tablet;

(v) at least one glidant in a total amount of about 0.1% to 1% by weight based on the total weight of the tablet;

(vi) at least one lubricant in a total amount of less than about 0.1% to 2% by weight based on the total weight of the tablet; and

(vii) a coating, wherein the coating further comprises a polymer; and,

wherein the tablet possesses a disintegration time of 5-10 minutes when measured by a standard USP disintegration test.

Claim 30. (New): A tablet for oral administration according to claim 29 comprising,

97.81mg microcrystalline cellulose PH101;

116.64mg microcrystalline cellulose PH102;

14.58mg poly vinyl pyrrolidone K-30;

45.36mg crospovidone;

0.65mg pluronic F68;

3.24mg aerosil;

9.72mg magnesium stearate; and,

19.44mg opadry blue coating.

REMARKS

All original pending clams, 1-24, are withdrawn without prejudice. Claims 25-30, presented herewith, are new.

Picture claims

All original pending claims are withdrawn, without prejudice, to expedite prosecution of the species, i.e., finished drug product "picture", claims presented herewith.[1]

Prior formulation

The only formulation of deferasirox previously on the market, EXJADE®, were dispersible tablets for oral suspension, in three dosage strengths, 125mg, 25 mg and 500mg.[2]

Lowering the dose

Deferasirox tablets of the presently claimed subject matter are formulated to exhibit slow release and, unexpectedly, much higher bioavailability. The proper therapeutic dose is accordingly identified by the Applicants to achieve certain efficacious exposure levels. The suitable dose, formulated as described and claimed by the Applicants, of deferasirox is now found to be 90 mg, 180 mg, and 360 mg per claimed tablets unit dosage. Characteristics of the new tablets for oral administration including disintegration time and rate of dissolution are uniquely required to reach the certain, tried and true, efficacious exposure levels.

---

[1] Narrow subject matter of the finished drug product is derived from original claim 17.

[2] Must completely disperse tablets by stirring in water until a fine suspension is obtained. Disperse doses of less than 1g in 3.5 ounces of liquid and doses of 1g or greater in 7 ounces of water.

The now claimed formulation, JADENU™, received accelerated FDA-approval based on a reduction of liver iron concentrations and serum ferritin levels.

The disclosed dosage formulation of deferasirox, now claimed, describes the only FDA-approved once-daily oral tablet for iron chelation to simplify treatment administration and improve compliance for patients with chronic iron overload.[3]

The Applicants respectfully submit that finished drug product "picture" claims 25-30 are in condition for allowance.

* * *

The Examiner is kindly encouraged to telephone the undersigned in order to expedite this case. No new matter has been added. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 02-2556. Applicants further authorize the Commissioner to charge any future deficiencies or credit any overpayment associated with the prosecution of the present application to the same.

Respectfully submitted,

/Patrick H. Higgins/
PATRICK H. HIGGINS
Attorney for the Applicants
Registration No. 39,709
(215) 851-8533
phiggins@eckertseamans.com
ECKERT SEAMANS CHERIN & MELLOTT, LLC
Two Liberty Place
50 South 16th Street, 22nd Floor
Philadelphia, PA 19102

[3] Chronic iron overload is a life-threatening cumulative toxicity that results from blood transfusions required to treat sickle cell disease, myelodysplastic syndromes, thalassemia and other conditions.

Exhibit F

Applicant-Initiated Interview Summary	Application No. 14/198,872	Applicant(s) GHOSH ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ADAM C. MILLIGAN*. (3)_____.

(2) *PATRICK H. HIGGINS*. (4)_____.

Date of Interview: *05 January 2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *25-30*.

Identification of prior art discussed: *U.S. Pre-Grant Publication (2012/0196909)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants' representitive discussed possible claim amendments to place the claims in condition for allowance Examiner agreed that changing claims 26, 28 and 30 to "consisting of" type claims to exclude the additional components taught by the prior art would render the claims free of the prior art. To overcome the a 112 2nd paragraph rejection for wrongful use of a trademark in a claim, Examiner suggested removing the trade names from the claims. Applicants' representitive agreed with the suggestions and appoved an Examiners Amendment to the claims to make the discussed amendments.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/ADAM C MILLIGAN/ Primary Examiner, Art Unit 1612	

Exhibit G

Notice of Allowability	Application No. 14/198,872	Applicant(s) GHOSH ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *See Continuation Sheet*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *26,28 and 30*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 8/28/14
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20160105* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

Continuation Sheet (PTOL-37) **Application No. 14/198,872**

Continuation of Item 1. This communication is responsive to : preliminary claim amendments dated 12/15/2015 and the first action interview.

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Patrick H. Higgins on 1/5/2015.

The claims have been amended as follows:

Claims 1-25 are cancelled without prejudice.

Claim 26. A tablet for oral administration **[[according to claim 25 comprising]]** **consisting of 90 mg deferasirox;**

[[24.45 mg avicel PH101]] **53.61 mg microcrystalline cellulose;**

[[29.16 mg avicel PH102;]]

3.65 mg poly vinyl pyrrolidone K-30;

11.34 mg crospovidone;

0.16 mg **[[pluronic F68]]** **poloxamer**;

0.81 mg **[[aerosil]]** **fumed silica**;

2.43 mg magnesium stearate; and **[[,]]**

4.86 mg **[[opadry blue coating]]** **seal-coat**.

Claim 27 is cancelled without prejudice.

Claim 28. A tablet for oral administration **[[according to claim 27 comprising]]** **consisting of 180 mg deferasirox;**

[[48.91 mg avicel PH101]] **107.23 mg microcrystalline cellulose**;

[[58.32 mg avicel PH102;]]

7.29 mg poly vinyl pyrrolidone K-30;

22.68 mg crospovidone;

0.32 mg **[[pluronic F68]]** **poloxamer**;

1.62 mg **[[aerosil]]** **fumed silica**;

4.86 mg magnesium stearate; and **[[,]]**

9.72 mg **[[opadry blue coating]]** **seal-coat**.

Claim 29 is cancelled without prejudice.

Claim 30. A tablet for oral administration **[[according to claim 27 comprising]]** **consisting of 360 mg deferasirox;**

[[97.81 mg avicel PH101]] **215.45 mg microcrystalline cellulose;**

[[116.64 mg avicel PH102;]]

14.58 mg poly vinyl pyrrolidone K-30;

45.36 mg crospovidone;

0.65 mg **[[pluronic F68]]** **poloxamer**;

3.24 mg **[[aerosil]]** **fumed silica**;

9.72 mg magnesium stearate; and **[[,]]**

19.44 mg **[[opadry blue coating]]** **seal-coat**.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: the above amended claims are allowable over the prior art because the picking and choosing of components and amounts from the prior art required to arrive at the instant claims would be too excessive to be considered *prima facie* obvious. It is further noted that Applicants have demonstrated improved patient compliance using the claimed dosage.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication should be directed to ADAM C. MILLIGAN at telephone number (571)270-7674.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

Exhibit H

FDA U.S. FOOD & DRUG ADMINISTRATION

[redacted]

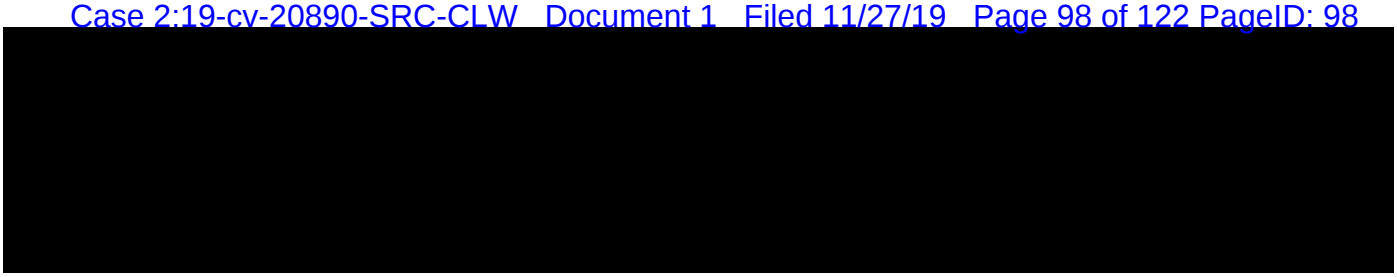
[redacted]

[redacted]

[redacted]

[redacted]

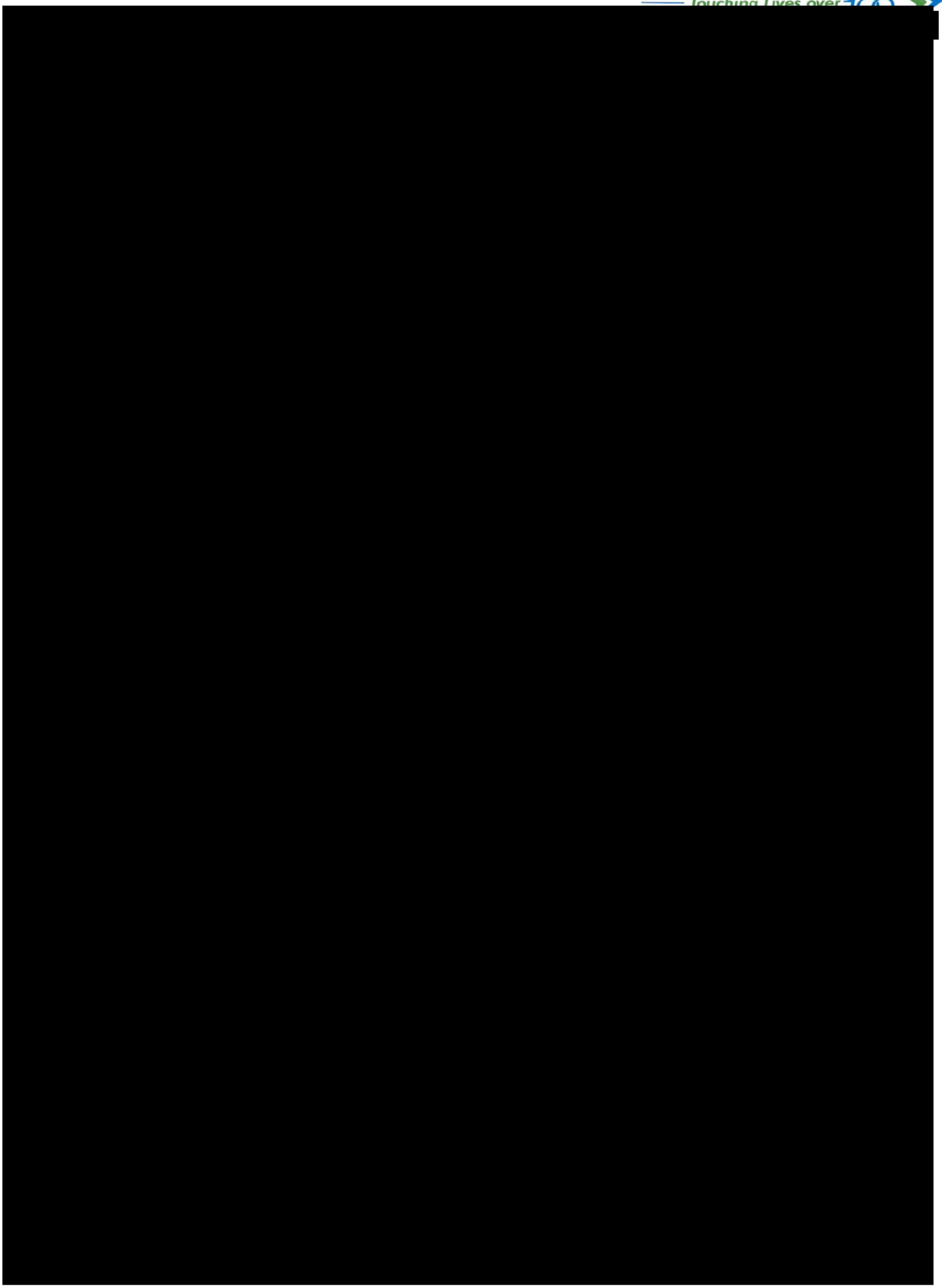
[redacted]

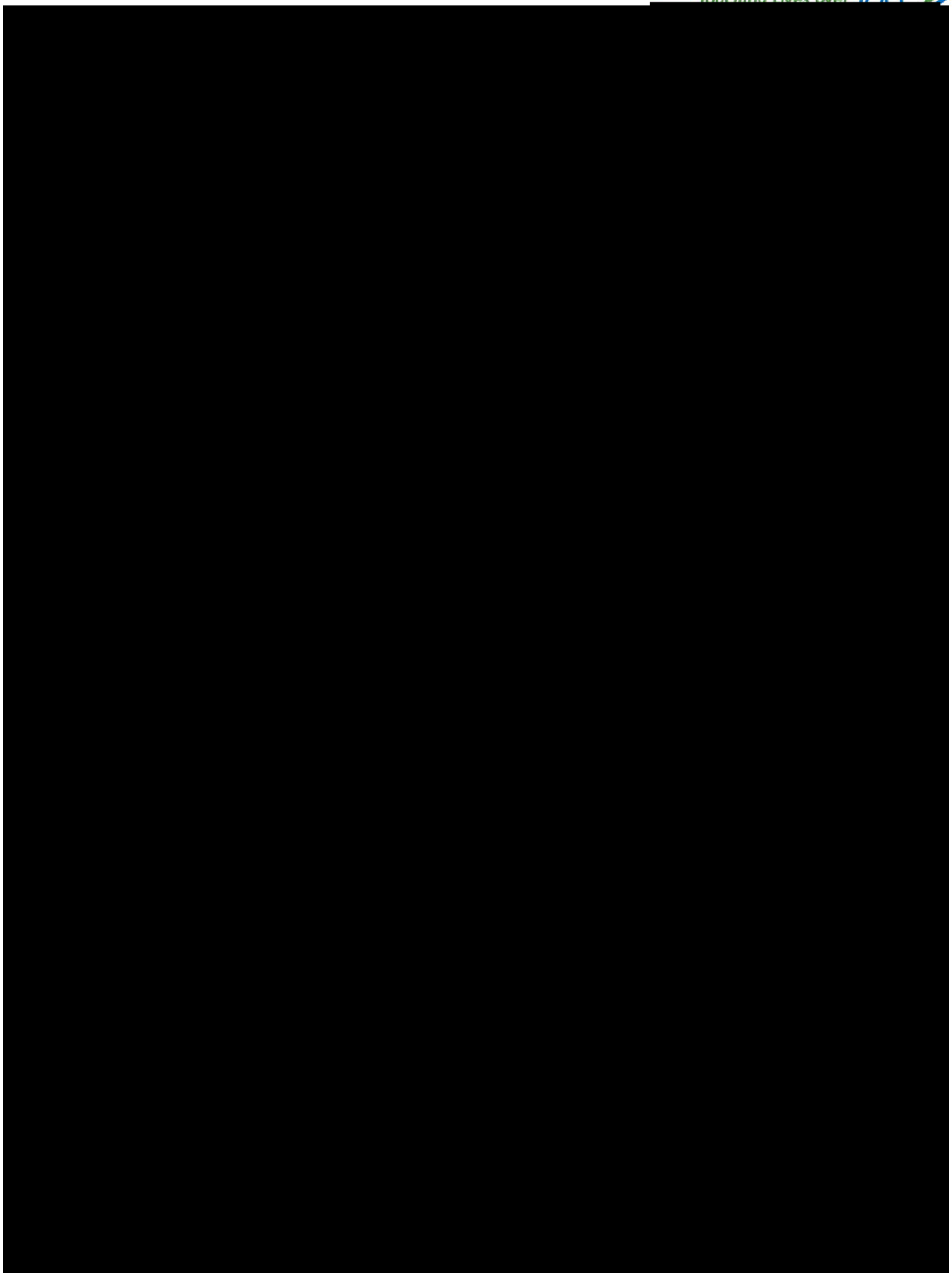


[redacted]

Exhibit I

Exhibit J





Sign In

FedEx® Tracking

716329295847

Ship date:		Actual delivery:
Mon 6/04/2018		Wed 6/06/2018 9 18 am
CHICAGO, L US	Delivered *Signed for by: H.JC*	BASEL CH

Travel History

▲Date/Time	Activity	Location
- 6/06/2018 - Wednesday		
9:18 am	Delivered	BASEL CH
8 54 am	On FedEx vehicle for delivery	ARLESHEIM CH
8:10 am	At local FedEx facility	ARLESHEIM CH
1:47 am	International shipment release - Import	BASEL CH
1:47 am	In transit Package available for clearance	BASEL CH
- 6/05/2018 - Tuesday		
10:17 pm	At destination sort facility	BASEL CH
8 07 pm	Departed FedEx location	ROISSY CHARLES DE GAULLE CEDEX FR
6:44 pm	Arrived at FedEx location	ROISSY CHARLES DE GAULLE CEDEX FR
6 00 am	In transit	INDIANAPOLIS, IN
5 04 am	Departed FedEx location	INDIANAPOLIS, IN
3 52 am	In transit	INDIANAPOLIS, IN
1:12 am	Arrived at FedEx location	INDIANAPOLIS, IN
- 6/04/2018 - Monday		
9 00 pm	Left FedEx origin facility	CHICAGO, IL
6:17 pm	Shipment information sent to FedEx	

Shipment Facts

Tracking Number	716329295847	**Service**	FedEx International Priority
Weight	0.4 lbs / 0.18 kgs	**Delivered To**	Mailroom
Total pieces	1	**Total shipment weight**	0.4 lbs / 0.18 kgs
Terms	Shipper	**Department number**	23861
Shipper reference	1007919.00007	**Packaging**	FedEx Envelope
Special handling section	Deliver Weekday	**Standard transit**	6/06/2018 by 12:00 pm

Sign In

FedEx® Tracking

716329295825

Ship date:		Actual delivery:
Mon 6/04/2018		**Tue 6/05/2018 9:22 am**
CHICAGO, IL US	**Delivered**	EAST HANOVER, NJ US
	Signed for by: F.MONORE	

Travel History

▲Date/Time	Activity	Location
− 6/05/2018 - Tuesday		
9:22 am	Delivered	EAST HANOVER, NJ
8:54 am	On FedEx vehicle for delivery	EAST HANOVER, NJ
8:28 am	At local FedEx facility	EAST HANOVER, NJ
6:50 am	Departed FedEx location	NEWARK, NJ
2:40 am	Arrived at FedEx location	NEWARK, NJ
− 6/04/2018 - Monday		
9:28 pm	Left FedEx origin facility	CHICAGO, IL
6:17 pm	Shipment information sent to FedEx	
6:03 pm	Picked up	CHICAGO, IL

Shipment Facts

Tracking Number	716329295825	**Service**	FedEx Priority Overnight
Weight	0.5 lbs / 0.23 kgs	**Delivered To**	Shipping/Receiving
Total pieces	1	**Total shipment weight**	0.5 lbs / 0.23 kgs
Terms	Shipper	**Department number**	23861
Shipper reference	1007919.00007	**Packaging**	FedEx Envelope
Special handling section	Deliver Weekday	**Standard transit**	6/05/2018 by 10:30 am

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Modify Search (index.cfm?panel=0&drugname=JADENU)

Search Results for Proprietary Name, Active Ingredient or Application Number: *JADENU*

6 records returned

RX OTC DISCN

CSV Excel Print

Display 50 records per page

Search for text in the table:

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	DEFERASIROX	JADENU SPRINKLE	N207968 (results_product.cfm?Appl_Type=NA&Appl_No=207968)	GRANULE	ORAL	90MG		RLD		NOVARTIS PHARMACEUTICALS CORP
RX	DEFERASIROX	JADENU SPRINKLE	N207968 (results_product.cfm?Appl_Type=NA&Appl_No=207968)	GRANULE	ORAL	180MG		RLD		NOVARTIS PHARMACEUTICALS CORP
RX	DEFERASIROX	JADENU SPRINKLE	N207968 (results_product.cfm?Appl_Type=NA&Appl_No=207968)	GRANULE	ORAL	360MG		RLD	RS	NOVARTIS PHARMACEUTICALS CORP
RX	DEFERASIROX	JADENU	N206910 (results_product.cfm?Appl_Type=NA&Appl_No=206910)	TABLET	ORAL	90MG		RLD		NOVARTIS PHARMACEUTICALS CORP
RX	DEFERASIROX	JADENU	N206910 (results_product.cfm?Appl_Type=NA&Appl_No=206910)	TABLET	ORAL	180MG		RLD		NOVARTIS PHARMACEUTICALS CORP
RX	DEFERASIROX	JADENU	N206910 (results_product.cfm?Appl_Type=NA&Appl_No=206910)	TABLET	ORAL	360MG		RLD	RS	NOVARTIS PHARMACEUTICALS CORP
Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder

Showing 1 to 6 of 6 entries

Previous 1 Next

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 206910

Collapse All

JADENU (DEFERASIROX)
90MG — Marketing Status: Prescription

Active Ingredient: DEFERASIROX
Proprietary Name: JADENU
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 90MG
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N206910
Product Number: 001
Approval Date: Mar 30, 2015
Applicant Holder Full Name: NOVARTIS PHARMACEUTICALS CORP
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=206910&Appl_type=N)

JADENU (DEFERASIROX)
180MG Marketing Status: Prescription

Active Ingredient: DEFERASIROX
Proprietary Name: JADENU
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 180MG
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N206910
Product Number: 002
Approval Date: Mar 30, 2015
Applicant Holder Full Name: NOVARTIS PHARMACEUTICALS CORP
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=002&Appl_No=206910&Appl_type=N)

JADENU (DEFERASIROX)
360MG Marketing Status: Prescription

Active Ingredient: DEFERASIROX
Proprietary Name: JADENU
Dosage Form; Route of Administration: TABLET; ORAL
Strength: 360MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N206910
Product Number: 003
Approval Date: Mar 30, 2015
Applicant Holder Full Name: NOVARTIS PHARMACEUTICALS CORP
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=003&Appl_No=206910&Appl_type=N)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Product Details

Additional Information about Patents

- Patent information is published on or after the submission date as defined in 21 CFR 314.53(d)(5).
- Patent listings published prior to August 18, 2003, only identify method-of-use claims. The listed patents may include drug substance and/or drug product claims that are not indicated in the listing.
- As of December 5, 2016, an NDA holder submitting information on a patent that claims both the drug substance and the drug product (and is eligible for listing on either basis) is required only to specify that it claims either the drug substance or the drug product. Orange Book users should not rely on an Orange Book patent listing, regardless of when first published, to determine the range of patent claims that may be asserted by an NDA holder or patent owner.

Patent and Exclusivity for: N206910

Product 001
DEFERASIROX (JADENU) TABLET 90MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	6465504	04/05/2019	DS	DP			04/24/2015

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submissio Date
001	9283209	11/21/2034	DS	DP			04/11/2016

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	ODE-39	01/23/2020

View a list of all patent use codes (results_patent.cfm)
View a list of all exclusivity codes (results_exclusivity.cfm)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Product Details

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- As of December 5, 2016, an NDA holder submitting information on a patent that claims both the drug substance and the drug product (and is eligible for listing on either basis) is required only to specify that it claims either the drug substance or the drug product. Orange Book users should not rely on an Orange Book patent listing, regardless of when first published, to determine the range of patent claims that may be asserted by an NDA holder or patent owner.

Patent and Exclusivity for: N206910

Product 002
DEFERASIROX (JADENU) TABLET 180MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submissio Date
002	6465504	04/05/2019	DS	DP			04/24/2015

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submissio Date
002	9283209	11/21/2034	DS	DP			04/11/2016

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
002	ODE-39	01/23/2020

View a list of all patent use codes (results_patent.cfm)
View a list of all exclusivity codes (results_exclusivity.cfm)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Product Details

Additional Information about Patents

- Patent information is published on or after the submission date as defined in 21 CFR 314.53(d)(5).
- Patent listings published prior to August 18, 2003, only identify method-of-use claims. The listed patents may include drug substance and/or drug product claims that are not indicated in the listing.
- As of December 5, 2016, an NDA holder submitting information on a patent that claims both the drug substance and the drug product (and is eligible for listing on either basis) is required only to specify that it claims either the drug substance or the drug product. Orange Book users should not rely on an Orange Book patent listing, regardless of when first published, to determine the range of patent claims that may be asserted by an NDA holder or patent owner.

Patent and Exclusivity for: N206910

Product 003
DEFERASIROX (JADENU) TABLET 360MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
003	6465504	04/05/2019	DS	DP			04/24/2015

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
003	9283209	11/21/2034	DS	DP			04/11/2016

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
003	ODE-39	01/23/2020

View a list of all patent use codes (results_patent.cfm)
View a list of all exclusivity codes (results_exclusivity.cfm)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Product Details

Additional Information about Patents

- Patent information is published on or after the submission date as defined in 21 CFR 314.53(d)(5).
- Patent listings published prior to August 18, 2003, only identify method-of-use claims. The listed patents may include drug substance and/or drug product claims that are not indicated in the listing.
- As of December 5, 2016, an NDA holder submitting information on a patent that claims both the drug substance and the drug product (and is eligible for listing on either basis) is required only to specify that it claims either the drug substance or the drug product. Orange Book users should not rely on an Orange Book patent listing, regardless of when first published, to determine the range of patent claims that may be asserted by an NDA holder or patent owner.

Patent and Exclusivity for: N206910

Product 003
DEFERASIROX (JADENU) TABLET 360MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submissio Date
003	6465504	04/05/2019	DS	DP			04/24/2015
					Patent		

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Use Code	Delist Requested	Submissio Date
003	9283209	11/21/2034	DS	DP			04/11/2016

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
003	ODE-39	TREATMENT OF CHRONIC IRON OVERLOAD IN PATIENTS 10 YRS. & OLDER WITH NON-TRANSFUSION DEPENDENT THALASSEMIA (NTDT) SYNDROMES AND WITH A LIVER IRON CONCENTRATION OF AT LEAST 5 MG OF IRON PER GRAM OF LIVER DRY WEIGHT & SERUM FERRITIN GREATER THAN 300

View a list of all patent use codes (results_patent.cfm)
View a list of all exclusivity codes (results_exclusivity.cfm)

JS 44 (Rev. 06/17)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

Alembic Pharmaceuticals Ltd.

(b) County of Residence of First Listed Plaintiff Gujarat, India
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*

Lisa J. Rodriquez, Esq., Schnader Harrison Segal & Lewis, LLP
Woodland Falls Corporate Park, 220 Lake Drive East, Ste. 200
Cherry Hill, NJ 08002 - (856) 482-5741

DEFENDANTS

Novartis Pharmaceuticals Corp. and Novartis AG

County of Residence of First Listed Defendant Morris
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT	TORTS		FORFEITURE/PENALTY	BANKRUPTCY	OTHER STATUTES
☐ 110 Insurance	PERSONAL INJURY	PERSONAL INJURY	☐ 625 Drug Related Seizure of Property 21 USC 881	☐ 422 Appeal 28 USC 158	☐ 375 False Claims Act
☐ 120 Marine	☐ 310 Airplane	☐ 365 Personal Injury - Product Liability	☐ 690 Other	☐ 423 Withdrawal 28 USC 157	☐ 376 Qui Tam (31 USC 3729(a))
☐ 130 Miller Act	☐ 315 Airplane Product Liability	☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability		PROPERTY RIGHTS	☐ 400 State Reapportionment
☐ 140 Negotiable Instrument	☐ 320 Assault, Libel & Slander	☐ 368 Asbestos Personal Injury Product Liability		☐ 820 Copyrights	☐ 410 Antitrust
☐ 150 Recovery of Overpayment & Enforcement of Judgment	☐ 330 Federal Employers' Liability	PERSONAL PROPERTY	LABOR	☐ 830 Patent	☐ 430 Banks and Banking
☐ 151 Medicare Act	☐ 340 Marine	☐ 370 Other Fraud	☐ 710 Fair Labor Standards Act	☐ 835 Patent - Abbreviated New Drug Application	☐ 450 Commerce
☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)	☐ 345 Marine Product Liability	☐ 371 Truth in Lending	☐ 720 Labor/Management Relations	☐ 840 Trademark	☐ 460 Deportation
☐ 153 Recovery of Overpayment of Veteran's Benefits	☐ 350 Motor Vehicle	☐ 380 Other Personal Property Damage	☐ 740 Railway Labor Act	SOCIAL SECURITY	☐ 470 Racketeer Influenced and Corrupt Organizations
☐ 160 Stockholders' Suits	☐ 355 Motor Vehicle Product Liability	☐ 385 Property Damage Product Liability	☐ 751 Family and Medical Leave Act	☐ 861 HIA (1395ff)	☐ 480 Consumer Credit
☐ 190 Other Contract	☐ 360 Other Personal Injury		☐ 790 Other Labor Litigation	☐ 862 Black Lung (923)	☐ 490 Cable/Sat TV
☐ 195 Contract Product Liability	☐ 362 Personal Injury - Medical Malpractice		☐ 791 Employee Retirement Income Security Act	☐ 863 DIWC/DIWW (405(g))	☐ 850 Securities/Commodities/ Exchange
☐ 196 Franchise				☐ 864 SSID Title XVI	☒ 890 Other Statutory Actions
				☐ 865 RSI (405(g))	☐ 891 Agricultural Acts
					☐ 893 Environmental Matters
					☐ 895 Freedom of Information Act
REAL PROPERTY	CIVIL RIGHTS	PRISONER PETITIONS	IMMIGRATION	FEDERAL TAX SUITS	☐ 896 Arbitration
☐ 210 Land Condemnation	☐ 440 Other Civil Rights	Habeas Corpus:	☐ 462 Naturalization Application	☐ 870 Taxes (U.S. Plaintiff or Defendant)	☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
☐ 220 Foreclosure	☐ 441 Voting	☐ 463 Alien Detainee	☐ 465 Other Immigration Actions	☐ 871 IRS—Third Party 26 USC 7609	☐ 950 Constitutionality of State Statutes
☐ 230 Rent Lease & Ejectment	☐ 442 Employment	☐ 510 Motions to Vacate Sentence			
☐ 240 Torts to Land	☐ 443 Housing/ Accommodations	☐ 530 General			
☐ 245 Tort Product Liability	☐ 445 Amer. w/Disabilities - Employment	☐ 535 Death Penalty			
☐ 290 All Other Real Property	☐ 446 Amer. w/Disabilities - Other	Other:			
	☐ 448 Education	☐ 540 Mandamus & Other			
		☐ 550 Civil Rights			
		☐ 555 Prison Condition			
		☐ 560 Civil Detainee - Conditions of Confinement			

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from Another District *(specify)* ☐ 6 Multidistrict Litigation - Transfer ☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
28 U.S.C. 1331, 1338 and 28 U.S.C. 2201, 2202

Brief description of cause:
Declaratory judgment seeking non-infringement

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:

JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions):

JUDGE Stanley Chesler DOCKET NUMBER 2:19-cv-12651

DATE 11/27/2019

SIGNATURE OF ATTORNEY OF RECORD /s Lisa J. Rodriguez

FOR OFFICE USE ONLY

RECEIPT # AMOUNT APPLYING IFP JUDGE MAG. JUDGE

Print Save As... Reset

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I.(a) **Plaintiffs-Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) **County of Residence.** For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) **Attorneys.** Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.Cv.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.
United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.
United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.
Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.
Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below**; NOTE: federal question actions take precedence over diversity cases.**)

III. **Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. **Nature of Suit.** Place an "X" in the appropriate box. If there are multiple nature of suit codes associated with the case, pick the nature of suit code that is most applicable. Click here for: Nature of Suit Code Descriptions.

V. **Origin.** Place an "X" in one of the seven boxes.
Original Proceedings. (1) Cases which originate in the United States district courts.
Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.
Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.
Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.
Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.
Multidistrict Litigation – Transfer. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407.
Multidistrict Litigation – Direct File. (8) Check this box when a multidistrict case is filed in the same district as the Master MDL docket.
PLEASE NOTE THAT THERE IS NOT AN ORIGIN CODE 7. Origin Code 7 was used for historical records and is no longer relevant due to changes in statue.

VI. **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553 Brief Description: Unauthorized reception of cable service

VII. **Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.
Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.
Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. **Related Cases.** This section of the JS 44 is used to reference related pending cases, if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.